REPORT
of the
COMMITTEE ON THE DRUG REVIEW PROCESS

Of the Science Advisory Board
to Health Canada

February 2000

REPORT OF THE SCIENCE ADVISORY BOARD COMMITTEE ON THE DRUG REVIEW PROCESS

PREFACE:

The Science Advisory Board was established in September 1997, by the Minister of Health, the Honorable Allan Rock. Its purpose is to advise the Minister on matters of science as they affect the Health Protection Branch (HPB) – and so the health of all Canadians – and to help foster public confidence in the HPB's work. Part of HPB's responsibilities includes the review and approval, or rejection, of applications by drug manufacturers to distribute new therapeutic products. This drug review process, which is designed to ensure that new drugs are safe and effective, has been criticized for being, for example, too slow and inefficient.

As a result, a number of committees and advisory groups have been set up to examine the process in detail; some reports and recommendations to improve the process have already been made. The Science Advisory Board wished to inform itself on the drug review process, and so it asked some of its members to look at the existing reports and the process itself, and to report back. The Board understands that its review was not exhaustive and that this is not a comprehensive report on the drug review process; it is, however, the consensus of its members and the recommendations we believe can be useful in the overall review process. The report of the Science Advisory Board's ad hoc committee on the drug review process follows, and I submit it to the Minister for his consideration.

My thanks to all the committee members for the report, and to those who helped them in their work.

Roberta Bondar,
O.C., O.Ont., M.D., Ph.D., F.R.C.P.(C.), FRSC
Chair of the Science Advisory Board

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COMMITTEE ON THE DRUG REVIEW PROCESS

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11. Glossary

REPORT OF THE SCIENCE ADVISORY BOARD COMMITTEE ON THE DRUG REVIEW PROCESS

1. Purpose

1.1 The purpose of this document is to report to the Science Advisory Board (SAB) on the activities of the Committee on the Drug Review Process, and to propose recommendations for action.

2. Background

2.1 The Committee was struck as an *ad hoc* Committee by agreement of the Science Advisory Board at its meeting of March, 1999, and was chaired by Doug Elliott. Members were Russ Graham, Jean Jones, Leslie Millin and Karen Semchuk, with Bernard Schwetz as an adviser. Dr. Semchuk and Dr. Schwetz were obliged to withdraw from the Committee's work part way through our activities because of other professional responsibilities.

2.2 In the SAB records of the March 1999 meeting, the Committee was to "proceed with a 'mini enquiry' into the HPB process to assess if the DRP work is credible and well informed, and to foster better management, as appropriate." A full statement of the objectives of our study is attached as Appendix A.

3. The Challenge

3.1 The Science Advisory Board was created in part to address the lack of public confidence in the work of the Health Protection Branch. Part of this lack of confidence springs from the perception that the process by which new drugs are approved is flawed. Critics of the drug review process have included some members of HPB's professional staff, as well as advocates

for various interest groups, representatives of industry, elected or appointed officials, and members of the public (some or all of whom we refer to as "stakeholders").

3.2 Some of the criticisms regarding the drug review process by interested persons are set out in Appendix B, especially regarding its transparency, timeliness, efficiency and effectiveness. These comments reflect the complexity of the process, and the differing expectations of the various stakeholders, including the general public. Such assertions are, in many cases, mutually contradictory. They cannot all be right, although they might very well all be wrong. We include them simply to show the diversity of opinion on the drug review process, without expressing any opinion as to their validity or lack of validity, except as set out in this Report.

3.3 We should note that clearly there *has* been improvement in timeliness, that some further constructive steps have been commenced in the area of consumer input, and that the relationship with the United States Food and Drug Administration's corresponding office is clearly productive, collegial, and one of mutual respect.

3.4 We wish to state categorically that the Committee has no evidence that persuaded us that unsafe drugs have been approved.

4. Work Method

4.1 We approached our work in various ways:

- ★ Creating, sending and reviewing questionnaires sent to stakeholders and to staff of the HPB;
- ★ Consultations with Dann Michols, the head of the HPB's Therapeutic Products Programme (TPP), the group which undertakes drug reviews, and with Mario Simard, General Counsel, Legislative Renewal, Transition, HPB, who respectively provided information on changes to the TPP and on the legislative renewal activity underway at Health Canada;
- ★ Consultations with officials of the Food and Drug Administration (FDA) of the United States, the Medicines Control Agency (MCA) of the United Kingdom, and the European Agency for the Evaluation of Medical Products (EMEA);
- ★ Contacts with the TPP Management Advisory Committee and with the Consultative Workshop on the TPP Drug Review process;
- ★ Direct discussions with informed stakeholders, including a meeting with key informants; and

★ Desk research.

4.2 Summaries of the questionnaire results are attached as Appendix B. They form the basis of many of our observations. Reports of the contacts with the US, UK and EU officials are attached as Appendix C, and they, too, have helped us with our work. We tabled an Interim Report part way through our work, to which SAB members responded, and it is attached as Appendix D. We have also attached, as Appendix E, a selected bibliography of previous studies and reports bearing on this subject. A brief summary of the law as it applies to transparency issues is Appendix F. The Report of the November 3-4, 1999 meeting with key stakeholders is attached as Appendix G. Finally, we have attached as Appendix H the draft EU legislation on Orphan Products, and Appendix I, the Report of the Consultative Workshop.

5. Observations

5.1 From our questionnaires, we learned:

★ Most respondents believe the process must improve its timeliness, efficiency, and effectiveness, and many fault it on transparency; but the Committee was not told and received no evidence that unsafe drugs are being approved;

★ A number of respondents criticized HPB management, and we draw the attention of managers to these criticism which are outside the scope of this Report as summarized in Appendix B;

★ Support for international harmonization is widespread, providing it means harmonization to the best international standards--not harmonization downward, as some have feared--and providing responsibility for the health and safety of Canadian citizens is not compromised;

★ No consensus exists on the policy of cost recovery, except perhaps that in its current manifestation it does not work well;

★ Post-market surveillance, or post-approval monitoring (both terms are used) or rather lack of it is seen as an important weakness.

5.2 From our consultations, we learned:

★ Generally, the results of the questionnaires were confirmed;

- ★ Many stakeholders feel urgently that the time for further review is past, that there is broad consensus even where stakeholders have very different philosophies (see the report of the Consultative Workshop on the TPP Drug Review Process, Appendix I, for example), and that the time for action is overdue;

- ★ Stakeholders agree that the process of legislative renewal provides the Department with a rare and valuable opportunity to transform at Health Canada the drug review process where necessary;

- ★ Scope for change is in some cases limited by existing Canadian legislation, which may be altered, and by international treaty obligations, which effectively may not.

5.3 From other jurisdictions, we learned:

- ★ Standards of transparency vary, but every jurisdiction has room for improvement;

- ★ No jurisdiction seems satisfied that it has dealt sufficiently effectively with post-market (post-approval) surveillance;

- ★ International harmonization is generally considered desirable;

- ★ There appears to be increasing support for the value of specific programs dealing with the problem of Orphan Products;

- ★ User fees are widely imposed in various ways, but have organizational implications (the term "cost recovery" seems solely Canadian, and has a somewhat different but similar meaning);

- ★ Standards of timeliness seem to vary widely, but the variation diminishes when the basis of computation is considered.

6. Discussion

In our Interim Report (Appendix D), we identified the essential principles of ***Timeliness***, ***Transparency***, ***Efficiency*** and ***Effectiveness***, which are discussed below.

6.1 Timeliness

6.1.1 Timeliness is in large measure governed by the availability of financial and other resources, as we discuss in section 7. We note that much progress has been made in recent years in improving the timeliness of the review of applications--the major problem seems to reside in the accumulation

of applications that must wait unopened until managers and reviewers have time to address them. This time is designated by TPP as "hold time", or "backlog" by others. It seems in at least some cases to be too long--up to more than 150 days for a fast-tracked application--and the governing factor here clearly is lack of resources.

6.1.2 We believe more improvement is possible, for example, by the exchange of review findings --not automatic acceptance of regulatory outcomes-- with comparable agencies in other jurisdictions. We noted Health Canada's efforts towards international harmonization, but we feel there is merit in information exchange as a practical immediate alternative to setting international standards, a long-term proposition. Another possibility is to share responsibilities with international partners, agreeing--for example--to capitalize on Canada's research strengths in one or two specific areas in exchange for access to the findings from other jurisdictions of comparable scientific rigour in a range of other designated areas.

6.1.3 If the "hold time", or "backlog", is satisfactorily reduced, we are confident that new applications can be processed in a time scale that will stand comparison with other industrialized countries. Further, elimination will enhance public confidence in Health Canada. Strategies such as providing Notice of Compliance with conditions to any application that has been on hand for some specific period of time, has been approved in some combination of comparable jurisdictions, and can be supported by identical information as that supplied to those jurisdictions can be invoked, but a specific plan with adequate resources is essential. A target for eliminating this "hold time" might be 18 months. We stress that there must be no shortcuts in safety and effectiveness appraisal.

6.1.4 A particular area for improvement is the process by which Health Canada deals with applications for products that are clearly and urgently needed to deal with serious and sometimes life-threatening conditions. In principle, these are assigned "fast-track" status, and may be granted a Notice of Compliance with Conditions (NoCC). The Committee noted that this process is not harmonized with the FDA's equivalent system, despite the clear opportunity to save time. We can only conclude that the basis for the current distinction is to reduce demand on resources.

6.1.5 Other improvements are procedural. The EMEA reports success with standard templates for applications, electronically readable. Various stakeholders have pointed out that certain steps in the review process could be carried out in parallel rather than sequentially, since they have no particular impact upon each other. Another measure, suggested in one of our consultations, was that where an applicant fails within an agreed time to remedy an incomplete or defective application, that application should be removed from the stream until complete or corrected, and then accepted only at the end of the queue. The people who can best identify procedural improvements are those who work daily with the procedure, and an active program to solicit and reward useful suggestions from reviewers will build morale and yield immediate benefits based on

solid, professional experience. We understand that many of these improvements have been implemented or are under active consideration by TPP.

6.1.6 We considered mandated time frames for review completion. On balance, this seems a poor option, although we agree that general targets are desirable, simply because applications are so variable. Where one application is supported by two volumes of data, another may have sixty volumes. Multiplying the number of reviewers proportionately will not alone suffice--the complexities are simply too great, and only adequate time will ensure an acceptable review. Delays might be reduced by a system under which, after the application was validated for completeness, a target date or dates for the review process could be set, based on the individual characteristics of the application.

6.1.7 There are models which can be reviewed to establish ways to deal with administrative backlogs, such as the courts. Studies or pilot projects to determine the applicability of such models may be desirable.

6.1.8 We also believe that the findings of the Consultative Workshop on the TPP Drug Review Process deserve positive consideration. The SAB has not reviewed those findings in detail. The Committee has considered them; however, we did not participate in that process in its entirety. While we have a few reservations about some of the details, we agree with the spirit of their recommendations.

6.2 Transparency

6.2.1 In our view and that of many stakeholders, the current drug review process is unnecessarily opaque. Health Canada persists in maintaining a level of confidentiality that is inconsistent with public expectation and contributes to a public cynicism about the integrity of the process.

6.2.2 Two conditions are said to make a high level of confidentiality necessary. One is that domestic and international laws require it; the other is that without it manufacturers will not choose to introduce new products into the Canadian market, and Canadians in need of such products will consequently suffer. As to the first, we refer to Appendix F. It reviews the pertinent legislation and concludes that much more transparent practices are quite feasible within existing legislation; further, given the legislative renewal now being undertaken for Health Canada, there is little barrier to introducing any such legislative amendments as might be required. As to the second: we observed directly in Washington public hearings involving the same manufacturers and the same products involved in Canadian applications, with much greater disclosure not only at the hearings but far more widely and immediately on the Internet: details are included at Appendix C.

6.2.3 Transparency is essential to public confidence. We believe that HPB should set new standards of access to information at all stages of the drug review process, enhancing transparency and

public confidence. We perceived no justification for current levels of delicacy regarding "commercial confidentiality". We would note: (a) Canada can at least emulate the standards of openness of our nearest and largest trading partner: (b) New legislation should provide for public hearings where appropriate; (c) If a product has gone through the FDA's public hearing process, this information should become part of the TPP's NDA review process, and the applicant should be responsible for providing copies of transcripts and videotapes. Further mechanisms employing contemporary communications and other technologies can be sought to achieve even higher standards more efficiently--public hearings are not sufficient of themselves.

6.2.4 We feel a system that allows for public hearings as appropriate is desirable, but public hearings will not in themselves provide a sufficient level of transparency--other methods must also be used.

6.2.5 We strongly support an Office of Consumer Affairs and Public Involvement (OCAPI) for Health Canada that has the necessary resources to implement a vigorous program of information and consumer involvement using a diverse range of contemporary communications techniques. The SAB has already endorsed the OCAPI concept, and has recommended the position of a Chief Scientist who will also help in disseminating information to the public.

6.2.6 OCAPI can implement a broad outreach strategy that will provide information in a meaningful and accessible form, will enrich and augment the drug review process, and will contribute to re-building confidence in Health Canada. The SAB understands that Health Canada is actively engaged in this process.

6 .2.7 Health Canada must actively seek to inform Canadians as widely as possible about the drug review process. TPP should have its own specific strategy.

6.3 Efficiency & Effectiveness

6.3.1 Efficiency and timeliness are closely interwoven. A persistent example given to us, of inefficiency and time wasting, is Schedule F. Schedule F to the *Food and Drug Regulations* establishes a list of ingredients which must be treated as prescription drugs. Adding to or withdrawing an ingredient from the Schedule requires an amendment to the regulations, a burdensome and lengthy process. Legislative renewal affords the opportunity for correction, if correction is needed. We have no opinion on the validity of this concern, but those involved in legislative renewal may wish to consider this issue.

6.3.2 International harmonization should in the long term improve efficiency. In the meantime, this should not preclude or postpone short-term co-operative projects or joint ventures to explore the potential for mutual improvements in handling applications. Comparing experiences with standard, machine-readable templates for applications, for example, as already noted, might well

yield improvements in efficiency at negligible cost, and this is an area where TPP has useful experience.

6.3.3 We recognize and support Health Canada's efforts to pursue international harmonization. But we believe that this long-term process can be enhanced by more immediate agreements to exchange scientific findings between regulatory agencies on a bi-lateral or multi-lateral basis without prejudice, with the consent of the applicants involved and their undertaking to provide identical information to all jurisdictions. We stress that this does *not* imply harmonization of approvals.

6.3.4 When the cost recovery policy was originally broached with the industry, it was seen as potentially contributing to efficiency. This the industry told us has not been the case. Industry has called upon the Treasury Board for a general moratorium on the Federal Government cost recovery policy pending a full review. The sums involved are large: of the $25.3-million currently spent by TPP on pre-market review of all drugs (both pharmaceuticals and biologics), some $20.9-million is derived from industry. TPP has initiated a review of cost recovery, whose results are expected next year.

6.3.5 Comparing expenditures on the drug review process across jurisdictions is difficult, because of variations in mandate. But the FDA spends about US$220-million (C$320-million) on New Drug Applications (NDA), of which US$85-million (C$123-million), or 36 per cent is derived from user fees. TPP advises that it spends C$25.3-million on pre-market review of drugs, of which C$20.9-million, derives from cost recovery, or over 82 per cent.

6.3.6 In other jurisdictions, the equivalent of cost recovery is described as "user fees". This may be a more accurate term, since it suggests a less tight relationship between what is levied and what is delivered. The FDA user fee of US$250,000 for each new drug application (NDA) is only loosely linked to the actual cost of reviewing an application. For one thing, not every FDA application goes to a public hearing, and the cost of a public hearing adds to the actual cost of reviewing, yet the fee is the same. For another, the income from user fees is added to existing revenues, whereas in the Canadian case cost recovery income has been largely substituted for appropriations. The UK experience suggests that a regulatory process could be entirely financed by user fees. EU officials consider a 75:25 ratio of user fee to appropriation is ideal. A 50:50 ratio would seem perhaps more acceptable in Canada, and this was the original intent; however, pending the outcome of the TPP review, we are not persuaded that the Treasury Board's cost recovery program for the drug review process has enhanced the efficiency of the process.

6.3.7 We are aware that a review of cost recovery has been launched by TPP. But public trust in Health Canada is eroded daily by current perception of the application of this policy; and the industry for quite other reasons equally dislikes the current policy. Over the short term, Health Canada should develop a strategy to inform the public on the clear, visible distinction between

cost recovery and the process of reviewing new products. Pending the outcome of the review of cost recovery, our committee believes that Health Canada should move to a 50:50 ratio as between cost recovery fees and appropriations, with a view to reducing the proportion of cost recovery in future. Subject to what may be learned from that cost recovery review process, we are of the opinion that a policy position should be taken--and expressed, if necessary, in the forthcoming legislation– that revenues from cost recovery will never exceed Parliamentary appropriations for the drug review process.

6.3.8 Post-approval surveillance is a weakness in all jurisdictions, posing serious challenges for rigorous scientific follow-up of approval decisions. Canada should move energetically in this area not only to implement the strategy designed by TPP, but to embrace pilot projects with well-defined groups to assess both risks and benefits in diverse, actual situations. This will be a valuable supplement to appropriate pre-approval clinical trials.

6.3.9 The drug review process is efficient in that it delivers the desired outcome at minimal cost and effort; it is effective in that it delivers the desired outcome with maximum benefit. Maximum benefit, we can see from Krever *et al.*, means that safety and well being of the person must take precedence over considerations of commercial advantage or bureaucratic process. We believe that if the drug review process is to be effective, it must engage public confidence. It must be seen to be credible, and based on sound science.

6.3.10 A well designed post market surveillance (or post-approval monitoring) strategy seems essential to efficiency in the drug approval process. We noted in our Interim Report that such a system would help ensure that the quality of applications and the thoroughness of investigation would be enhanced, to the improvement of efficiency.

6.3.11 A comprehensive strategy for post market surveillance has been developed for the HPB, and the most important thing is simply for Health Canada to fund it (perhaps with some appropriate industry contribution), and get on with it.

6.4. Orphan Drugs

6.4.1 Orphan products, which benefit a very small but intensely needy segment of the population, typically are not brought to market by major manufacturers because the cost of development and introduction do not justify the financial return. This market-driven approach, while fully justifiable in terms of current business assessment techniques, means that Canadians in acute need of help will not have access because they are too few.

6.4.2 We were impressed with the FDA's Orphan Products program in the United States, and also impressed with the initiatives now working their way towards implementation in the European Union. Something similar was proposed for Canada in the 1992 Gagnon Report, but the official

response was that it was unnecessary--that existing programs would suffice. We are less certain. A specific program, blending incentives, would bring new innovative talents into the therapeutics market, would add to Canada's exportable innovations, would offer opportunities for international joint ventures (especially with Europe). More important, it would confirm in the public mind Health Canada's commitment to the health protection of *all* Canadians, including those whose needs are sufficiently rare as to escape the normal attention of the market.

6.4.3 This recommendation of the Gagnon Report should now be implemented. There are opportunities for international synergy and co-operation in this area with the EMEA, the FDA and Japan. TPP should bring forward a suitable program of industry incentives, for which appropriate funding will be needed. Administration through the Canadian Institutes for Health Research merits consideration.

7. Resources

7.1 There is virtually unanimity that the drug review process has insufficient resources. But the problem is not simply one of money. There are general problems of human resources, as well as human resource problems that are specific to a science environment. There are general financial problems, and there are problems arising from the Treasury Board's cost recovery policy. There are also problems of what we might call administrative resources, by which we mean that managers have access to too few tools, or options, to shape their work. And, of course, all these problems are interactive.

7.2 An example of lack of resources is the drug review process "hold time". Eliminating this, as noted above, would greatly ease many of the concerns over timeliness. HPB staff have asserted that if this could be cleared, the time for processing most applications would fall within the acceptable bracket for industrialized countries. Public confidence in the process will be enhanced if it can be clearly seen that applications are processed in a timely way, and applicants will have some assurance that the business benefits from investing in a drug will not be put at risk due to a slow or inefficient process. While financial and personnel resources must be brought to bear here, some additional administrative resources, in the form of additional procedures, would also be helpful. For example, it has been suggested to us that where other comparable jurisdictions have already reviewed a new product, HPB might well--with the agreement of the applicant--take advantage of the work of others and issue Notices of Compliance with Conditions, subject to some agreed period during which any outstanding concerns might be addressed so that full NoCs can in fact be issued, an administrative option not now available.

7.3 Similarly, OCAPI as proposed to the SAB potentially offers additional administrative resources to address questions of transparency and effectiveness, at the very least. The SAB has already endorsed the policy work done in this regard. Public expectation is high, and action is needed.

7.4 More generally, it is clear that the government's budget reduction exercises have diminished human resources well beyond what any manager could have anticipated or wanted. Despite measures that have been partly successful in improving efficiency, the lack of resources and regular criticism of TPP cannot be conducive to good staff morale. Low morale in turn is likely to impair optimum efficiency. We have noted with concern the comments on morale at TPP expressed in the report of an external consultant[1].

7.5 Study after study has confirmed what scientists have empirically known for a very long time: critical mass is essential to effective scientific work. They must have the time and opportunity to interact; and they must have professional resources upon which they can draw. They must have the opportunity to live and work as scientists: to publish, to scrutinize the work of others, to communicate not only electronically but through the time-proven practice of participating in scientific meetings. The benefits to be derived from allowing scientists to develop their scientific careers in this way cannot be overstated.

7.6 In recommending to the Minister the appointment of a Chief Scientist, the SAB believed that this should be a priority. He or she should be given the mandate and resources to establish a critical mass of credible scientists who can participate in the review process as quickly as possible. Achieving critical mass and scientific credibility will be achieved much more quickly and efficiently if done in conjunction with Canada's academic medical community. Health Canada should enhance its collaboration with the clinical and academic medical community; enhancing and maintaining effective ties requires attention and resources.

7.7 Core scientific competency is the top priority. Health Canada will neither attract nor retain the best and brightest without a professional ambience in which scientists can meet challenges with appropriate infrastructure, publish freely and face peer review just as freely, and pursue the highest scientific productivity, within the constraints of a federal regulatory mandate. The potential for interactive work through the Canadian Institutes for Health Research (CIHR) may expand TPP's horizons, not to re-introduce direct research within TPP, but rather to ensure that TPP scientists can be allowed and indeed encouraged to spend a portion of their working time in research with colleagues elsewhere to enable them to retain and hone their professional skills, and pursue professional advancement.

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[1] PricewaterhouseCoopers, Therapeutic Products Program: Baseline Assessment of Drug Submission Review Process, pp. 79 - 80, April 26, 1999.

7.8 We have noted with concern, and have had it pointed out during consultations, that the number of acting positions among senior science managers in the HPB is extremely high, and that some of these positions have remained filled by acting personnel for years at a stretch. We have also been advised that even where a position has been authorized and the salary and benefit funds are not in doubt, it typically takes up to two years to staff the position. This is unacceptable. Funds must be found, for salaries, equipment and other necessities of scientific work, or not only will it be difficult to recruit the best scientists that Health Canada needs, but it will be hard to retain the best it already has.

7.9 No consideration of resources can avoid the question of the Treasury Board's cost recovery policy. We will not repeat our earlier discussion other than to say that the current application of this policy is unsatisfactory: to the industry, to consumers, and to TPP managers. Cost recovery, however implemented, cannot be a substitute for adequate parliamentary appropriations.

8. Recommendation

We recommend that the Minister obtain the necessary funding in order that Health Canada managers can implement the following recommendations:

8.1 Give priority in allocating resources to enhancing the professional scientific capacity of Health Canada.

8.2 Immediately allocate resources to address pending applications.

8.3 Allocate adequate funding to ensure acceptable timeliness in all applications.

8.4 Establish a priority-review system for urgently needed new products that is harmonized with the FDA system.

8.5 Enhance transparency in the drug review process.

8.6 Establish the Office of Consumer Affairs and Public Involvement without further delay, and provide it with the necessary resources.

8.7 Design and implement a broad communications strategy on the drug review process.

8.8 Expedite international exchange of scientific findings with key partners.

8.9 Design and implement a post-approval strategy.

8.10 Re-visit cost recovery.

8.11 Develop an Orphan Products program.

8.12 Give positive consideration to the recommendations of the Consultative Workshop on the Therapeutic Products Programme Review Process.

9. Thanks

9.1 We wish to thank all who helped us in this task, and especially Dr. Bernard Schwetz, whose aid was invaluable. Respondents to our questionnaires have our deep appreciation. And thanks must

go to the Secretariat of the Science Advisory Board and the staff of the Health Protection Branch whose help allowed us to complete our task in time.

Appendix A

Objectives of the Drug Review Process Study by the Board[1]:

An independent study of the drug review process within HPB, to determine how it is perceived by interested parties, to identify strengths and weaknesses , real or perceived, and to reach conclusions/ make recommendations for improvement. The following lines of inquiry have been determined in the letter to interested parties.

1. Timeliness, efficiency and effectiveness of the drug review process, in general and the identification of how could it be improved?

2. The adequacy/appropriateness of the priority drug review process. Whether it is operating in a principled, timely, efficient and effective way? and how it could be improved

3. Fairness, reasonableness and timeliness of the public's access to information about drug submissions and about drug safety and efficacy? and warranted changes?

4. The appropriateness of Health Canada's harmonization and cooperation with foreign governments regulatory authorities for the drug review process? and under what conditions?

5. Cost recovery, and concerns that charging fees for drug review may unfairly influence the drug review process? how to alleviate concerns?

6. Principles which should guide the drug review process.

In essence, the Committee of the SAB will proceed with a "mini inquiry" into the HPB process to assess if the DRP work is credible and well-informed, and to foster better management, as appropriate. The Committee will consider the views of a wide range of interested parties and may include a field visit to the United States to hear first hand the views of Federal officials, industry and other key parties representing public views. Information from these parties in other countries, for example from Europe and Australia, will be sought in writing.

The Committee will provide the Board with periodic progress reports, outlining its directions, for endorsement as appropriate. It will produce an interim Report by September 1999 and a final Report by November 1999, for endorsement by the Board prior to presentation to the Minister.

[1] The Science Advisory Board endorsed at the May 1999 meeting

Appendix A

The working of the Committee.

Guiding principles:

The Committee's work will be evidenced-based. It is committed to providing the best possible independent advice to the Minister and to HPB as they work to protect the health of Canadians.

Scientific and socio-economic relevance will be assessed by the Committee. It will comprise Members that have extensive appreciation of the key issues involved in the DRP. If SAB Members are not available, the Committee will secure scientific advice possibly through external scientific expert advisors. Alternatively, the Committee may commission additional studies, possibly through research assistants or other contractual agreement, provided this is in keeping with the Board's terms of reference and the confidentiality of the information.

Written submissions from interested parties will be reviewed in terms of comprehensiveness and credibility and relevance to the lines of inquiry.

Openness, fairness and transparency will be reflected in the Committee's working approach. It will strive to be efficient in allocation of its resources. Consequently, the Committee will give serious consideration to the options of hearing directly from interested parties – this may involve Committee meetings or Board sessions, as appropriate. Interested parties will be advised of the Board's approach.

The Committee will function under the general direction of the Chair of the Committee, and with the full knowledge of the Chair of the Science Advisory Board (possibly through cc's).

The Committee will report on its findings and recommendations through periodic status reports as well as a final report, for the SAB's consideration and endorsement.

As the Committee's recommendations and conclusions will help strengthen the current drug review process in Canada, it will be appropriate to maintain open communications with the management of the Health Protection Branch, in particular the Therapeutic Products Programme. (TPP)

In view of the Senate Report on rbST and the Office of the Auditor General's comments on the DRP, the Committee will endeavour to keep these organizations informed of its study, its objectives, findings and conclusions.

Strategies to progress with the study, including the consideration of scientific advisors external to the SAB.

Time lines and milestones should be defined to project the work of the Committee and to outline expectations for the Board.

Generally, the Committee aims to deliver a draft status report for the September 1999 SAB meeting and a draft final report for the November 1999 SAB meeting.

The Secretariat of the SAB will keep interested parties, including the TPP, advised of the Committee's progress in this study.

Any external scientific expert advisor invited to join the Committee must do so under the same terms and conditions as the Board Members. (e.g. remuneration, travel expenses, conflict of interest, etc). Advisor(s) bring in-depth appreciation of the scientific validity and relevance of issues raised by interested parties and of their proposed recommendations.

Similarly, terms and conditions for any contractual agreements for research assistance will be in accordance with federal policies and the terms of reference of the Board.

Appendix B

DRUG REVIEW PROCESS SURVEY
May 1999
Updated June 1999
with the addition of respondent names, editorial changes and the addition of respondents 30 d and 32

Question 1

Is the drug review process, in general, timely, efficient and effective? If not how could it be improved?

7 - Canadian Medical Association (CMA) believes the drug review process needs improvement. Institute formal post-marketing studies for efficacy and safety in a real population of patients who may have other diseases. (CMA attached a letter of June 8, 1993 re the Gagnon report with 3 of 5 paragraphs stressing the need for improved post-marketing programs.)

9 - Canadian Treatment Advocates Council believes that HPB performance in the review of anti-viral drugs compares poorly with other countries in the developed world and that the following changes are needed:

a) To ensure timeliness mandate enforceable timelines "Rolling Review". Canada should follow FDA lead in having informal pre-submission consultation and affording the opportunity of sponsoring companies to provide emerging data on on-going research to the regulator during the course of the review;
b) HPB should conduct reviews concurrently rather than sequentially: don't wait for clinical studies to review the chemistry and manufacturing data;
c) Maintain continuity of staff and contact persons assigned to reviews. Companies seem to deal with different people each time they communicate with HPB about a review;
d) HPB submission formatting requirements should be consistent with those of other countries;
e) HPB should harmonize its reviews of submissions with other countries;
f) HPB should monitor the long term safety and effectiveness of licensed drugs and provide the information which is generated to consumers;
g) Not certain that HPB has sufficient financial resources, sufficient expertise among staff, or that current resources are effectively managed, or policies and procedure are conducive to timeliness, efficiency and effectiveness.

10 - The Canadian Cancer Society is not aware of information which could help guide answers to this question other than individual anecdotes. Insufficient information to give a broad response to questions 1 and 3.

11 - Canadian Diabetes Association believes that the review process is not timely and efficient. Effectiveness is in question. Canada has longest time frame (16 months) compared with US (12), Sweden (5), Switzerland (7), Germany (7) and UK (5). In 1997, 46 new molecular entities launched; Canada was never mentioned as a country of first launch. The Association suggests standardizing Canadian requirements to match other international jurisdictions and the review of other successful regulatory systems.

12 - Canadian Aids Society sent 3 papers along with response. Papers: 1) position statement on reforming drug review process, September 1998, 2) "Timeliness and Transparency: Assessing the review process for HIV Drugs" November 1998, and 3) Advocacy Update: Reform of the Drug Review Process at HPB September17, 1998
Response to question 1:

a) review the priority review policy so that all anti-viral HIV drugs are covered
b) streamline the bureaucracy;
c) increase resources devoted to the review of human prescription drugs;
d) alter accounting procedures to permit carryover of unused funds to the following year
e) strive for more transparency;
f) adapt a policy of rolling reviews (see 9 b));
g) convert current review targets to firm commitments and introduce mechanisms to ensure time lines are met.

13 - Canadian Drug Manufacturers Association:

- Review process for generic drugs neither timely nor efficient;
- Three bar charts for 32 different submissions appended. Submission consists of 2 review streams: chemistry and manufacturing (C&M), and safety and efficacy (S&E). C&M lags far behind S&E reviews;
- Review times slower than other countries (see 11);
- Increase staff to review C&M. All reviewers must be trained and supervised to increase consistency in decision making;
- Reviewers, managers, and directors must be accountable for timely action and adherence to performance targets.

14 - Canadian Society of Hospital Pharmacists:

Positive response – process felt to be generally timely, efficient and effective. One concern – backlog where backlog is the time a submission sits in a queue before being assigned for review.

15 - Canadian Healthcare Association (CHA) is aware of industry concerns. CHA believes industry's concerns must be addressed in the light of needed overarching principles for HPB and serious misgivings regarding the cost-recovery process.

16 - Canadian Health Food Association:

- No. Where a drug has been accepted by other governments with similar standards of health care as Canada, consider a conditional permit to market the drug in Canada pending final evaluation by HPB experts;
- Cost recovery should be reviewed. No penalty for government not meeting performance standards as there is for industry to meet specified time lines;
- The impact of cost recovery on consumers, industry etc is being currently dealt with in another department but should be evaluated under the umbrella of this Drug review process;
- Drug Review process not transparent. Boundaries between over the counter (OTC) drug claims vs prescription drug claims not clearly defined, especially for traditional herbal remedies. Company could spend millions of dollars for OTC claim only to have it rejected and told it is a prescription claim;
- Standards of evaluation need to be clearly defined and made available to all interested parties.

17 - Canadian Health Coalition - No direct response.

18 - Canadian Hemophilia Society - No direct response.

21- Canadian Pharmacists Association noted improvement in timeliness of process but still slow compared internationally. Also notes difficulties pharmacists face when a drug is accepted in the US and not in Canada (Viagara, AIDS medications). Impact on pharmacists twofold: placed in position of trying to explain the delay, loss of clientele since many go to the US for prescriptions.

23 - Canadian Public Health Association comments that the process and staff disadvantaged due to human resources policies; need more staff resources and ways to attract and retain quality staff

25 - Canadians for Health Research cannot answer definitively. Feedback suggests lack of clinical expertise is one of the problems.

28- Consumers' Association of Canada:
System must be sensitive to the rapid requirements for new drugs to the critically ill, but cautious in approving for the healthier population where there may little or no evidence of medical need.

(forget the patents and economic gains; look at products representing new advances in pharmacology and technology)

30 d - FDA provides a documented account of their experience with the concepts of timeliness and efficiency, and notes the necessity to factor both FDA and industry time. (Charts referenced: "New Drug Development" and "Generic Drug Approvals")

31 - GPIM – the Quebec-based group of pharmaceutical manufacturers:
Don't change the law; improve the organization and process. Use data from other agencies.

32 - Heart and Stroke Foundation of Canada comments on principles: question 6

33 - Medical Reform Group:
Timeliness only important when dealing with drugs representing important advances over existing products, post marketing surveillance of new drugs for safety is abysmal in Canada and US (cites ref. for critique of US system), adopt a medical need criteria i.e. new drugs approved only if superior to existing products on the market (see 28)

36- Nonprescription Drug Manufacturers Association:

- No. Review of OTC non-prescription takes longer now than in 1996. Particular concern is review of the chemistry and manufacturing data;
- Review of drugs undergoing a switch from prescription to non-prescription drugs should be considered priority and resources allotted accordingly. Takes 18 months to remove ingredient from Schedule F of the F & D Regs. Too long. **Urge SAB to recommend to the Minister that an alternative to Schedule F be developed;**
- When cost recovery introduced HPB agreed to an accountability process to rebate fees if targets not met. Industry unable to assess efficiency. **Urge SAB to recommend to Minister an Office of Self-Care be established within TPP and staffed by reviewers trained to assess OTC drug submissions.** (Two Bureaus, Nonprescription Drugs and Human Prescription Drugs amalgamated into one: Bureau of Pharmaceutical Assessment) Further recommend:
  a) industry and government work together to develop reasonable and rationale review times;
  b) assure scientific and regulatory competency of all staff through training;
  c) establish individual performance targets for all staff and link to salary and other incentives so targets achieved or surpassed;
  d) use attestation to approve monographs for lower risk products combined with establishment licences to replace pre-market assessment with same notification system used for devices and cosmetics.

38 - The Parkinson Foundation of Canada believes that generally this process seems to proceed in a timely fashion, with HPB conscientiously trying to expedite matters. Are there mechanisms in place whereby amendments to approved protocols could receive expedited review approval?

40 - Patented Medicines Prices Review Board:
A great deal of commentary. One suggestion seems to be the implementation of HC's proposal for a drug product licensing framework involving re-evaluation of drug products i.e. more regulatory control? (Patented Medicines Prices Review Board). Also suggests new drug be compared to safety and efficacy of other standard therapies.

41 - Pharmaceutical Manufacturers Association of Canada:
No. Lists the process shortcomings relative to self-established performance targets and international times for review. Learn from other jurisdictions. Perhaps an Agency with sufficient resources to do the job.

42 - Provincial Ministries of Health (Nova Scotia) is unable to comment on the question but is concerned drugs get to market with insufficient information to determine whether they are better than current therapies.

45 a – Dr. Holbrook comments that the response will depend on stakeholder.
Drug approvals lag relative to other countries. Very few breakthrough drugs with a high impact on quantity or quality of life. A reasonable system should be in place to identify such drugs and allowing fast tracking of their review. Rather than attempt to alter median drug review times, develop a hierarchy of priority for review.
For faster drug reviews 4 key points must be addressed:

a) adequate personnel – high level of training in the basics; unlikely current contingent is sufficient; HPB makes poor use of large contingent of scientific expertise across Canada;
b) cost – additional personnel or use of external experts costs money. A drug approval agency somewhat separate from government (more similar to FDA) might well be an improvement;
c) adequate post-marketing follow up; a faster drug approval process should only be considered if a rigorous post-marketing monitoring system has been established;
d) rigor of work and relative freedom from bias – These principles should override any process developed.

45 b - Dr. Noni MacDonald - HPB does not have breadth nor depth for internal reviews, final decisions often rests with senior bureaucrats who may not appreciate discordant views.

45 c - Dr. John Gill believes that there is need for more staff. There is fickle support of management for staff. Hire more skilled internal reviewers; contract out some work. Legal framework for licensing differs in Canada and US – public should be informed of differences, for transparency let sponsoring company and HPB reviewers present findings to an advisory committee in a public forum.

47 - Merck-Frosst feels that the process not timely, efficient or effective:

- Since Gagnon report of 1992 restructuring has resulted in a net reduction of scientists at both the review and managerial levels, and the issuance of innumerable guidelines, policies and guidance documents;
- The chemistry and manufacturing reviews begin after target performance deadlines have expired;
- Merck-Frosst suggests:
  a) create a first-rate independent Canadian Drug Regulatory Agency staffed with highly qualified well motivated scientists. The Agency should be adequately supported with public funds and fees would be levied from pharmaceutical companies. The mandate should be to review submissions and rapidly approve innovative therapeutic products;
  b) Increase use of external peer experts;
  c) Increase partnerships with other major regulatory authorities;
  d) Foster the harmonization requirements with the EU and USA; this includes harmonization of content requirements for submission and of the general format of submissions to be in line with the format accepted by other countries.

Generalize the Use of Computer-Assisted Drug Submissions – 5 Merck reviews of products have already been done with this technology.
Include in the Canadian Food and Drugs Act definite time limits for the review of drug submissions.

48 - Canadian Association for Population Therapeutics comments on the need for a systematic evaluation of medications after they are marketed. (post-marketed drug evaluation) Urges a system of conditional approvals. HPB should have access to data that would allow the on-going evaluations of drugs on the market.(Has many more comments)

49 - Multiple Sclerosis Society of Canada:
Since 1993 reviews of 2 of 4 drugs for MS were significantly delayed compared to other countries. Reviews of the other 2 occurred within a reasonable time period. Since 1998, further delays of a "fast tracked" drug have occurred.

65 - Federal/Provincial/Territorial Pharmaceutical Issues Committee does not respond directly to the six questions. Please note that this response is signed by two persons one of whom responded

to some of the questions with the exception of this one and question 2 and 6 – refer to Provincial Ministries of Health (Nova Scotia), number 42 above.

Question 2

Is the priority drug review process operating in a principled, timely, efficient and effective way? If not, why not, and how would you improve it?

7 - CMA suggests that the process could be enhanced by setting up an Advisory Committee on Medicine. This might result in greater input by practising physicians and greater transparency.

9 - Canadian Treatments Advocates Council suggests HPB should rewrite its policy on priority review so that it encompasses all HIV antiviral drugs. The wording of the FDA priority review policy should be adopted and HPB should interpret the policy the same as FDA.

10 - Canadian Cancer Society suggests that specific criteria be available for determining entrance into the priority review process. The priority review process should clearly describe the evidence benchmarks required for efficacy given that the drug may be early in its evaluation. Furthermore, success at the expedited review process should be followed with a full formal review when further evidence becomes available and using same benchmarks as used for regular review process.

11 - Canadian Diabetes Association notes the need for clarification of requirements for priority review. Only 2 applications received priority review in 1998 compare to 28 other applications. Canadian Diabetes Association understands priority review targets 6 months time frame for notice of compliance. If 6 months is correct then process clearly not functioning in a timely fashion.
Targets for review process should be reassessed and firmly established.
Reviewers must be held accountable for time frames. (Same point made before: see Summary Question 1 last point under heading HPB Staff)

12 - Canadian AIDS Society considers priority drug review process not working well especially for AIDS drugs:

- No HIV drugs received priority review since 1996 due to restrictive criteria and current policy;
- FDA priority review policy requires only that the new drug …. *demonstrate the potential to address unmet needs* , whereas Canadian policy requires ….*a significantly improved efficacy or significantly diminished risk over existing therapies…for a disease or condition that is not adequately managed by drug marketed in Canada*, a much narrower definition;
- Revise current priority review policy criteria;
- Take into account the needs of (AIDS) individuals requiring leading edge medications to achieve an optimum standard of living.

13 - Canadian Drug Manufacturers Association has no comments to this question.

14 - Canadian Society of Hospital Pharmacists – no comment.

15 - Canadian Healthcare Association – no comment.

16 - Canadian Health Food Association – no comment.

17 - National Health Coalition – no direct response.

18 - Canadian Hemophilia Society – no direct response.

21 - Positive. Canadian Pharmacists Association comments that priority drug review process seems to be working well.
It seems resources needed for priority review are taken away from review of non-priority drugs.
Important to increase TPP capacity if and when priority drugs need additional work.

23 - Canadian Public Health Association understands that "priority" products are new active substances. Does HPB have the expertise needed? Arrange with other professionals and regulators to bring efficiencies to the Notice of Compliance process.

25 - Positive. Canadians for Health Research (CHR) - This cannot be accessed externally.
Assumes that system in place and that the need for scientific manpower and sufficient financial resources are monitored and problems rectified when necessary.
CHR questions how contracting out of drug reviews will guarantee a more principled, timely, efficient and effective review system.

28 - Consumers' Association of Canada believes that questions 2 and 3 can be answered in combination. An open, transparent, accountable system, which includes consideration of social and ethical issues, would improve the priority drug review process as well as change the public's access to information about drug submission and drug safety and efficacy.
Priority review should be based on the need for the drug, not necessarily the demand. One criterion for prioritizing should be that its benefit is based on therapeutic versus enhancing normal functions. Also consider cost of medication to consumers.

30 d - FDA comments that concerning the "priority drug" timeliness of review, note the "accelerated approval" section the chart entitled "New Drug Development".

31 - GPIM – the Quebec-based group of pharmaceutical manufacturers – no comment.

32 - Heart and Stroke Foundation of Canada comments on principles: question 6.

33 - Medical Reform Group question: Who decided on the principles of priority drugs. Were they subject to public and open discussion? Is there any mechanism in place for an open review of these principles?

36 - Nonprescription Drug Manufactures Association of Canada – no comment.

38 - Positive. The Parkinson Foundation of Canada considers that the priority review process operates in a principled, timely, efficient and effective way.

40 - Patented Medicine Prices review Board has suggested that a brief summary of the basis for approval of new products analogous to the FDA Disclosure Summary should be available to the public, as should the rationale for granting priority review. All scientific evidence forming the basis of for an approval decision should be publicly accessible.(This is also in response to Question 3)

41 - Pharmaceutical Manufacturers of Canada. Supports concept of priority review policy but notes reviews are same as regular review except somewhat faster.
Priority reviews take place to the detriment to regular review process.
Suggest design a more efficient system for review of all drugs.
Status of a review should be maintained throughout the review of a submission i.e. through first review, and when necessary through second reviews.
Timelines for priority reviews often not met.
Countries with efficient, timely drug approval systems enjoy higher economic benefits and more dollars for researchers and the research infrastructure.

42 - Provincial Ministries of health (Nova Scotia) – no comment.

45 a - Dr. Holbrook – no comment.

45 b - Dr. Noni MacDonald: Concerns (my wording) who makes the decision re priority status and has HPB the expertise to make the decision and review the product. There needs to be better information for the public on how "fast tracking occurs". HPB may want to think about possible conflict of interest issues – this relates to whether HPB has the breadth and depth of expertise to rapidly review a high priority drug without there being any conflict of interest.

45 c - Dr. John Gill: Priority drug review established to allow agents offering major new therapeutic advances to jump the queue for a rapid review. Process being abused (my wording and

interpretation because every company believes or claims to believe their product offers new advantages etc..) The fervour for priority review stems from a belief that regular review is too slow.

47 - Merck-Frosst reports that in December 1996, recommendations were made by the Director General of the Drugs Directorate to allow Priority Review status to be granted to a drug submission for:

- *A serious, life-threatening or severely debilitating disease or condition, for which there is substantial clinical evidence that the drug provides effective treatment, prevention or diagnosis of a disease or condition for which no drug is presently marketed in Canada;*
- *Significantly improved efficacy or significantly diminished risk over existent therapies;*
- *Preventatives or diagnostic agents for a disease or condition that is not adequately managed by a drug marketed in Canada.*

Two of five Merck-Frosst drugs granted priority status.

Suggestions:

1. The process of granting priority status should be more transparent.
2. A general improvement in efficiency of the approval system would likely reduce the number of priority reviews and limit the procedure to the appropriate cases.
3. In order to alleviate the risks inherent in speedy priority approvals, emphasis could be placed on the development of post-marketing tools.

48 - Canadian Association of Population Therapeutics has not seen effectiveness of priority review system.

HPB policy does not seem to have evaluation criteria that would establish whether there is a risk-benefit profile for a drug to differentiate it from other drugs as a candidate for priority review.

The predicted increased regulatory burden of adding "new indications" to acceptance criteria for priority review (policy announcement February 18, 1997) seems to be leading HPB into an operational dilemma that may weaken the review system.

49 - Multiple Sclerosis Society of Canada gave an example of a priority drug which after 180 days of fast-track review is still not complete despite the fact that there is no other therapy in Canada. Suggests that HPB look very closely at working with similar review agencies in the US and Europe to expedite reviews.

65 - Federal/Provincial/Territorial Pharmaceutical Issues Committee does not respond directly to the six questions. Please note that this response is signed by two persons one of whom responded

to most of the questions with the exception of this one and question 1 – refer to Provincial Ministries of Health (Nova Scotia), number 42 above.

Question 3

Do you feel that the public has fair, reasonable and timely access to information about submissions and about drug safety and efficacy? If not, what changes do you feel are warranted?

7 - CMA states that public has limited access to information about new drug submission and about the efficacy and safety issues.
Information about new drug submission could be publicised (newspapers and consumer publications – Canadian insert to Consumer reports)

9 - Canadian Treatment Advocates Council states that the public has no access to information about drug submissions. In contrast, FDA conducts public hearings on new drug submissions and the deliberations and assessment, including comments by individual panel members, becomes a matter of public record.
The amount and quality of information is inadequate.
Post-marketing data (my interpretation) only superficial. HPB should demonstrate its commitment and allocate sufficient resources to the performance of this work (in this context, I believe "work" refers to the post-marketing program)

10 - Canadian Cancer Society not aware of information which could help guide answers to this question other than individual anecdotes. Insufficient information to give a broad response to questions 1 and 3.

11 - Canadian Diabetes Association understands that drug submission information is confidential until a Notice of Compliance is issued. Only at that time that consumers are made aware of new products and the appropriate consumer information is received. Any inordinate delays in review process would compromise the concept of "fair, reasonable and timely access to information".
Standardize all information available on a new drug and make such information available to all consumers.

12 - Canadian AIDS Society does not believe that the public has any real access to information about drug submissions.
Even companies have difficulties determining review status of drugs contrasted with the open forum approach of FDA (transparency)
Product monographs available to consumers (I question this ??) but the Society argues that the information should be available in a variety of formats.
Stronger tracking of drugs after approval. I interpret this as meaning a stronger post-marketing program.

13 - Canadian Drug manufacturers Association believes that public information on approved generic drugs is not warranted Such information would be of little value since the same safety and efficacy information would be available on its brand name counterpart which would have been approved 12 years earlier.

14 - Canadian Society of Hospital Pharmacists believes that this question also related the question 2 on priority drugs for which it had no comment. The greatest area for improvement is transparency. Benefits of transparency include demystifying the process so that stakeholders will be aware of how the process works, how fees are structured, what the principles are and why the process is equitable Other examples of transparency benefits cited.

15 - Canadian Healthcare Association – no comment.

16 - Canadian Health Food Association states "No" not if the public is defined as the end user of the product:

- Further comments that drug monographs which are available would be difficult to understand and frightening. Information should be user friendly and presented in a clear and consistent easy to understand format;
- Comments also that information presented to the consumer is usually of the tone that "gov't is in bed with the pharmaceutical industry" which does not lead to consumer confidence in the drugs being used;
- Information should be developed by independent experts who can present an unbiased package for consumers.

17 - National Health Coalition – no direct response.

18 - Canadian Hemophilia Association – no direct response.

21 - Canadian Pharmacists Association notes that there are 2 parts to the question: access to information on drug submissions, and access to information on drugs.
Access to information on submissions only available after approval; difficult to comment on fairness etc.
CPA publishes the Compendium of Pharmaceutical Specialities based on product monographs.
Suggests TPP reconvene meeting with CMA, Consumers, CPA and disease specific groups to discuss streamlining processes for patient information.

23 - Not an issue for Canadian Public Health Association. National Advisory Panel on Risk/Benefit Management of Drugs final report identified the need and made recommendations re compilation and dissemination of info to consumers, health professional and "experts".

25 - Canadians for Health Research believes that the public gets no information from HPB about drug submissions or drug safety and efficacy, unlike the U.S. FDA, which identifies drugs under review, provides extensive information on newly approved drugs, and CHR believes, drugs that have been rejected. Disclosure of this information would ease the public's perception that HPB operates in complete secrecy.
CHR is also dismayed that Health Canada has not responded to some of the very serious allegations made in the popular press. This contributes to further erosion of public confidence in HPB.

28 - Consumers' Association of Canada believes that questions 2 and 3 can be answered in combination:

- An open, transparent, accountable system, which includes consideration of social and ethical issues, would improve the priority drug review process as well as change the public's access to information about drug submission and drug safety and efficacy;(added to Question2)
- An open and transparent system must provide opportunity for public input at the outset and include mechanisms to deal with consumer complaints;
- Priority review should be based on the need for the drug, not necessarily the demand. One criterion for prioritizing should be that its benefit is based on therapeutic versus enhancing normal functions. Also consider cost of medication to consumers. (added to Question 2)

30 d - FDA has undertaken a major effort to reach the public as part of the Food and Drug Modernization Act. The FDA seeks citizen input through public meetings and has placed information on the internet (http://www.fda.gov/)

31 - Positive response from GPIM – the Quebec-based group of pharmaceutical manufacturers. The group expresses concern over the role government and the news media as sources for credible information. Perhaps drug companies should make the announcement when their products are approved.

32 - Heart and Stroke Foundation of Canada comments on principles: question 6.

33 - A resounding NO from the Medical Reform Group. And that applies to health professionals as well. Safety and efficacy data submitted by companies are regarded as proprietary and released only with the companies' permission. Access to Information (30 day's time limit) resulted after 21 months in only 5 pages of a 300 page study – all data blanked out:

- System should be changed to be similar to the US system where companies cannot prohibit the release of such health and safety information and responses for information are usually received within 10 working days;

- Adopt US approach to advisory panels which permit the right of public input from the start. (Canadian expert committees generally do not consider individual drugs - are not open and minutes posted are vague and leave out most of the important discussion that took place)

36 - Nonprescription Drug Manufacturers Association believes the public would be better served by examining the issue of direct-to-consumer advertising of prescription drugs. Suggests that government more widely publicise their Websites: Canadian Adverse Reaction Newsletter, HPB Information Letters, Alerts, Warnings, and Press Releases. **The association urges SAB to recommend to the Minister that Canada not disclose submission filing dates, similar to practices in other jurisdictions.**
Regarding drug safety and efficacy, the public is provided with safety information on the label of over-the counter-drugs (OTCs). Similar information on prescription drugs is available from health professionals.

38 - The Parkinson Foundation of Canada believes the general public has little knowledge of drug review process or requirements. There are misconceptions regarding the role of the regulator, physicians and the pharmaceutical industry. Cites example of drug being removed from the market and no statement made to the public to guide patients and their families, in the process of contacting their neurologist, how to proceed in discontinuing the use of the drug etc.... Need more educational information.

40 - Patented Medicines Prices Review Board cites TPP Special Access Program concerning new drug submissions under review. Availability of such information would be helpful to the PMPR Board to monitor patent status of new drugs:

- Suggests use of internet as a media for information on therapies which are or will be available in Canada. Has also suggested that a brief summary of the basis for approval of new products analogous to the FDA Diclosure;
- Summary should be available to the public, as should the rationale for granting priority review. All scientific evidence forming the basis for an approval decision should be publicly accessible. (This is also a partial response to Question 2 re priority drug review)

41 - Pharmaceutical Manufacturers Association of Canada in general is **not** in favour of providing information to the public without the sponsoring company's consent. PMAC suggests the following options:

- Inquiries received regarding the status of a specific drug could be referred to the sponsoring company which could provide the information or a rationale for not doing so (information is the property of the sponsor not TPP);
- The company could provide TTP with written consent to provide information on all or some of the dates associated with the submission;

- TPP could consider the applicability of the FDA pre-approval public hearings approach where FDA decision-makers and their expert advisors are publicly questioned about their conclusions related to specific submissions and when such panels are used;
- TPP could consider making transcripts of TPP Expert Advisory Committee meetings available to the public;
- Makes the point that product monographs are available.

42 - Provincial Ministries of Health (Nova Scotia) believes that even if the information was available, most members of the public not aware of it. The drug review process still very much misunderstood by the public.

45 a - Dr. Holbrook feels the response to this from all sides is a resounding **no**. The public has a right to know. HPB requires a more open, streamlined and accountable access to information program - easily accomplished in today's electronic world. (It is possible that only the characteristic reserve and residence (?) and trust etc has kept the government from unexpected liability.)

45 b - Dr. Noni MacDonald: This is the area most needing of upgrading. Suggests an active post-marketing surveillance for all new drugs and careful review of serious adverse effects by an independent review panel – this information can then be made available to public both lay and non lay.

45 c - Dr. John Gill: To date the public has not had adequate or timely information re drug submissions. Date of submission, applied for indications and the stage of review should be made widely available to all interested parties. The final detailed review, if contentious, should be undertaken in an open forum. Only through such transparency can the review process be achieved.

47 - Merck-Frosst has three comments:

1) Availability of product monographs to physicians and the inserts in every package of drug should provide all information required for the safe use of the drug;
2) The current legislation and regulations make it difficult for the public to access information on drug submissions. Requests for such information meet with considerable resistance from the industry because of the danger of communicating proprietary and confidential information. The perception is that the system is used mainly to gain a competitive edge;
3) Suggests that the information disclosed primarily demonstrate the transparency of the approval process – e.g. reasons for approving the drug, verification by peer experts.....

48 - Canadian Association for Population Therapeutics has basically two comments:

1) Information on drugs currently in clinical trials is lacking. Information from publications and on the internet should permit HPB to be more inclusive;
2) It would greatly benefit the public if HPB offered some publication on outcomes of their reviews and updated information on the safety and efficacy of drugs as this becomes available during the marketing life of the drug. Canadian Adverse Reaction Newsletter is the only publication attempting to do this. Precedents for regulatory agency publications can be found in several countries including the UK, Australia and Sweden.

49 - Multiple Sclerosis Society of Canada has three comments:
1) Status of review process should and could be made much more transparent;
2) Difficult to obtain information on the status of drug submissions. Often more information available from the company whose drug is under review than from the publicly-funded agency doing the review;
3) Information on drug submissions, current updates on drug safety and efficacy should be made available through a variety of media including the Health Canada web site.

56 - Federal/Provincial/Territorial Pharmaceutical Issues Committee does not respond directly to the six questions. Please note that this response is signed by two persons one of whom responded to most of the questions – refer to Provincial Ministries of Health (Nova Scotia), number 42 above

Question 4

Should Health Canada continue to pursue harmonization and cooperation with foreign governments' regulatory authorities for the drug review process? If so, under what conditions?

7 - CMA supports the concept of international harmonization of submission processes provided that the product under consideration is reviewed independently by Canadian authorities, and ideally by the proposed Advisory Committee on Medicine, at the conclusion of the submission process and prior to granting a notice of compliance.

9 - Canadian Treatment Advocates Council believes greater harmonization and cooperation with other countries should reduce the time required to prepare and review submissions. Also suggests that HPB should investigate innovative solutions more aggressively - evaluate what countries like Sweden and Australia are doing to speed up the review process.

10 - The Canadian Cancer Society has a number of comments:

- harmonization and cooperation makes sense and would avoid duplicating the review of the same information already reviewed by other countries' federal regulatory agencies;
- To ensure that HPB could harmonize with other countries, there would need to be some form of credentialing process whereby there is a commonality to the intensity and breadth of review. The review of manufacturing practices, for example, could be a possible area with a similar perspective in different countries;
- Harmonization might provide HPB with an international leadership opportunity by helping develop a template for the consolidated review of drugs that would be held in common by several countries willing to participate in this multinational process. Each country would be able to individualize their review of a drug by adding to this common body of information.

11 - Canadian Diabetes Association supports harmonization and cooperation with other regulatory authorities but notes that currently the drug review process in Canada is not harmonized, and an independent assessment of each new drug is undertaken by Health Canada:

- The Association also states that all countries should receive the same information on new drug submissions – the benefit being efficiencies in cooperating and sharing information on new drug submission requests for further information. Since Canada appears to be comparatively slower in its approval process, Canada would need to be equipped to respond in an efficient manner by strict adherence to timelines with dedication of appropriate and adequate resources to achieve this result;
- Canada should recognize international expertise already used in specific countries awarding initial approval and launch of a new drug.

12 - Canadian AIDS Society supports harmonization and cooperation with foreign regulatory agencies:

- It notes that for the past several years, Canada is already involved, as an observer, in an International Conference on Harmonization (ICH) exploring ways to harmonize the drug review process on an international level.

  Suggested areas to pursue include:

  1) conducting more joint reviews with other regulatory agencies; and
  2) eliminating our own system of drug review and rely on other countries instead. (cites Timeliness and Transparency: Assessing the review Process for HIV Drugs, November 1998 – a report attached to the letter of response.)

13 - Canadian Drug Manufacturers Association: "Yes, Health Canada should be prepared to accept the review outcomes of jurisdiction approval to the same standard and be prepared to develop expertise in niche areas where the differences in review standards can be clearly supported scientifically."

14 - Canadian Society of Hospital Pharmacists agrees that harmonization should be pursued. Health Canada MUST be satisfied that other authorities operate under similar principles, in an effective, ethical manner, and that the results from other jurisdictions are of high quality and result in minimizing risks to Canadians.

15 - Canadian Healthcare Association: " CHA believes that if Health Canada continues to pursue harmonization with other countries, that harmonization should not result in the lowering of standards used in the Health Protection Branch's risk management process."

16 - Canadian Health Food Association supports harmonization "as long as it is for the benefit of the end user, i.e. the consumer." "If the research has been done and /or reviewed by other regulatory bodies with similar health and safety standards as Canada then there should be recognition of this."

17 - National Health Coalition – no direct response.

18 - Canadian Hemophilia Society – no direct response.

21 - Canadian Pharmacists Association infers support and states that Canada must also be a full partner in endeavours such as the International Conference on Harmonization. (*Could this statement be related to the comment by the Canadian Aids Society (12) and the Medical Reform Group (33) that Canada is an* ***observer*** *at the ICH?)*

23 - Canadian Public Health Association supports harmonization and cooperation with regulators from other countries:

- If efficiencies can be obtained, pursue cooperative efforts. Canadians need to have confidence in manufacturers, quality of ingredients, quality control processes and in the regulatory review process used;
- Does not support less stringent controls on product safety than exist for Canadians today.

25 - Canadians for Health Research supports the concept of harmonization but is unable to suggestion under what conditions and comments that there may instances when clinical trials should be conducted in Canada?

28 - Consumers' Association of Canada is very wary of harmonization for a number of reasons:

- harmonized quality is generally towards the lowest common denominator.
- harmonization could lead to enforced and involuntary approvals under some of the terms of NAFTA and other trade agreements;
- Canada is presently only an observer to the present negotiations of the International Conference on Harmonization – the major players being the US, EU, and Japan and multinational pharmaceutical companies based in these countries. This is not a balanced representation and is viewed as favouring industry initiatives rather than a consumer benefit;
- Consumers insist that safety and efficacy be given primary consideration and that market issues be a secondary concern.

30 d - FDA comments on harmonization:

- HPB is an important representative to the International Conference on Harmonization (ICH);
- FDA considers the joint review process between Canada and the US to be extremely valuable, and efficient and effective for both countries;
- FDA and HPB work together to support WHO efforts in setting standards, developing reagents, providing technical consultations etc on areas affecting drug, vaccine, and blood safety issues, and biotechnology. Such cooperative endeavours are mutually beneficial in conserving resources.

31 - GPIM – the Quebec-based group of pharmaceutical manufacturers supports harmonization and suggests a global approach where smaller countries (Norway , Australia, New Zealand, Switzerland with comparatively high standards as Canada) could develop and maintain internationally recognized centres of excellence in one area of specialization. Regardless of the source of drug submission, it could be sent to the country with the appropriate area of specialized expertise for assessment and the review results accepted.

32 - Heart and Stroke Foundation of Canada comments on principles: question 6.

33 - Medical Reform Group: Current International Conference on Harmonization (ICH), to which Canada is an observer, conducted solely by regulatory authorities in the US, EU and Japan and the multinational pharmaceutical companies. Excluded are: generic companies, consumer groups, health professionals and regulatory authorities from developing countries. Purpose of ICH is to speed up drug approvals, not to try to enhance safety nor to free up resources to enhance development of new innovative therapies. Concerned that harmonization could lead to acceptance of lowest common denominator re safety and efficacy.

36 - Nonprescription Drug Manufacturers Association supports harmonization as long as the end result is faster approval of submissions, and notes that Canada is an observer at the International Conference on Harmonization:

- Concerned that ICH focuses on new chemical entities not over the counter drugs (OTCs). Suggests that Canada seek internationally accepted submission standards for drugs changing from prescription to nonprescription standards, and for drugs being developed for the OTC market. Better to accept a US or EU format than develop a Canadian submission format;
- Canada should "certify" regulatory authorities deemed to have a drug submission process equivalent to that of Canada. OTCs marketed in those certified countries would be permitted to be marketed in Canada without further pre-market approval of a submission.

38 - The Parkinson Foundation of Canada supports harmonization. HPB might consider foreign rulings to expedite the Canadian drug review process.

40 - Patented Medicines Prices Review Board – no comments.

41 - Pharmaceutical Manufacturers Association of Canada supports harmonization and notes that Canada continues to maintain different criteria for drug approval than exist in other countries:

- Canada has longstanding agreements with Sweden, Australia and the UK for the sharing of evaluation reports for new drugs. TPP maintains that these reports do not provide a substitute for, nor help, expedite submission assessment and the exact role of Performance Evaluation Reports (PERs) is not known;
- PMAC encourages Mutual Recognition Agreements (MRAs) with one or more respected countries to avoid sponsoring companies in Canada having to submit for total re-review data already assessed and pronounced on by another regulator(s);
- The use of MRAs can be beneficial - the impending 1998 Canada-EU MRA dealing with conformity assessments and certification of good manufacturing practices for manufacturing sites.

42 - Provincial Ministries of Health (Nova Scotia) supports harmonization but current standards should not be lessened.

45 a - Dr. Holbrook supports harmonization provided current principles are upheld. The concern on the academic side is that thresholds for approval not sink to the lowest common denominator but held at a high level for the safety and health of all. She is also concerned that international processes not disadvantage developing countries which may lack the resources to provide adequate drug approval themselves.

45 b - Dr. Noni MacDonald : Continue to pursue cautiously harmonization and cooperation with foreign regulatory authorities – caution needs to be considered for all harmonizations due to Canadian health care system which differs from others such as the US, UK, European countries and Japan. Post-marketing studies must be required to be done on Canadians (safety [adverse drug reactions], efficacy); notes also, re harmonization, that clinical study test populations differ genetically. Encourages paperwork requirements be made as similar as possible to reduce delays.

45 c - Dr. John Gill: In principle harmonization of reviews should be undertaken. This should not automatically necessitate or mandate recognition in Canada of drugs approved elsewhere. Acceptance of manufacturing reviews could be harmonized with other countries.

47 - Merck-Frosst indirectly supports harmonization by suggesting Canada elevate its review approval procedures to international standards now being set by the US and European countries. Secondly, Merk-Frosst urges the finalization and full implementation of Mutual Recognition Agreements (MRAs) with its major trading partners. The Canadian Regulator should become a major partner for other Regulatory Agencies and export its knowledge and expertise as well as benefit from partners' knowledge and expertise.

48 – Canadian Association for Population Therapeutics supports harmonization and observes that HPB must retain its independence recognizing that the first goal is the well-being and best medical treatment of Canadians. HPB should not be a blind follower of what others do. For example, the current proposal for a new drug licensing scheme for Canada (Product Licensing Framework III, TPP) tries to incorporate some of the principles of data requirements agreed in the International Conference on Harmonization (ICH) but the proposed requirements for post-market reviews by manufacturers will place considerable regulatory burden on HPB as well as affected manufacturers and will make Canada the only country, of which the Association is aware, that links such requirements to the licensing procedure. The Association believes that harmonization initiatives should be assessed on the basis of scientific rather than administrative merits. (Dr. Appel, who responded on behalf of the Association cites his own reference: Appel, W.C., Harmonization in regulatory pharmacovigilance: impracticalities and scientific irrationality, Pharmacoepidemiology and Drug Safety, 1998; 7: 359-361.

49 - Multiple Sclerosis Society of Canada supports harmonization provided the health and safety of Canadians, which are paramount, are not compromised.

56 - Federal/Provincial/Territorial Pharmaceutical Issues Committee does not respond directly to the six questions. Please note that this response is signed by two persons one of whom responded to most of the questions – refer to Provincial Ministries of Health (Nova Scotia), number 42 above.

Question 5.

Concerns have been expressed that charging fees for drug review may unfairly influence the drug review process. Do you have such concerns? If so, how could your concerns be alleviated?

7 - CMA supports cost recovery in principle:

- process should transparent and at arms length from industry;
- cost recovery procedures should not pose an impediment to new, effective. pharmaceuticals or to approval of new indications for existing medications;
- there is a concern over the appearance of conflict of interest. This could be alleviated by pooling fees charged to manufacturers making submissions and by not linking fees to time required for reviews – ensuring arms length transactions;
- if a company does not have the money to pay the fee, there should be provision for review of "orphan" drugs.

9 - Canadian Treatment Advocates Council:

- no economic incentive for HPB to review submissions in less time or to grant approvals;
- fees charged are not in any way linked to performance by the regulator;
- fees provide advantage of transferring the burden of cost from taxpayers to drug companies;
- no evidence that charging fees to sponsors results in a drug review process more responsive to the needs of pharmaceutical manufacturers.

10 - The Canadian Cancer Society expresses concerns over cost recovery:

- when a fee is levied there is a risk that the party paying the fee could unduly influence the process;
- a negative impact of levying fees would be that drugs which are viewed as being less profitable would be at risk to not go through the process at all. Some drugs or other devices are very valuable in improving health and yet are quite inexpensive;
- levying a fee directly for the HPB process could result in preferentially more expensive drugs and devices to be reviewed;
- charging of fees could be more susceptible to influence where the process is very costly for some drugs, relative to drugs where the process cost is substantially less costly and where no fees are charged;
- it would be better if all pay a fee or none pays a fee.

11 - Canadian Diabetes Association has a number of comments which do not seem to support users fees (cost recovery):

- understands that disbursement of fees is independent of the drug review process; reviewers have no contact with the fee process and that fees are paid whether a drug is approved or rejected;
- levying a fee is not the issue; the perceived problem rests in the fact that guidelines and timeframes are not consistently adhered to. This inconsistency could conceivably lead to a public perception that payment amount can influence expediency or outcome;
- The required payment is in essence a "fee for service". Service must be perceived to be consistent and satisfactory. Payment of fees should be linked to the assurance that the "right" resources are in place to undertake a "credible" review within a specific "timeframe". An accountability framework against these criteria must be established and monitored.

12 - Canadian AIDS Society has no strong concern over charging fees but offers a number of comments:

- fees should be used for the drug review process and not transferred to the general expenditures at year end;
- problem is lack of resources to fund TPP activities; deep budget cuts have adversely effected the ability of HPB staff to meet internal time lines as well as improve efficiency in drug review;
- a cost recovery program implemented to replace revenues lost through budget cuts has not been able to provide necessary resources to keep pace with increasing workload;
- outdated accounting procedures have meant monies accrued through cost recovery measures are lost to General Revenue at the end of the fiscal year, further undercutting resources available for drug review.

13 - Canadian Drug Manufacturers Association does NOT support cost recovery:

- No, because there is no need for the Regulatory agency to curry the favour of the industry since fees are charged to offset expenses incurred, not to satisfy the sponsor;
- The real concern is that the approval process is not accountable to the performance targets set for review;
- The fee process could be used both as a "carrot" and a "stick" to enhance and increase the quality of reviews.

14 - Canadian Society of Hospital Pharmacists' "concerns are not one of implementing a cost recovery policy, as those who will benefit financially from the sale of the product should bear the costs of ensuring the product is safe and effective".

- Cost recovery may encourage manufacturers to be correct the first time, saving time and resources of Health Canada and ultimately the taxpayer;
- Concerns lie mainly in the area of undue pressures exerted on reviewers;

- It must be made absolutely clear that the HPB mandate is to protect the health and safety of Canadians.

15 - Canadian Healthcare Association has identified two different but related issues regarding the charging of fees for drug reviews:

1. The need for adequate funding. Restore HPB's capacity to carry out independent investigative science and to lessen reliance on information provided by industry scientists. Other comments include the need to restore in-house investigative science requiring lab capacity and hiring of research scientists. Inadequate funding compromises the perceived independence of HPB. A total of 5 paragraphs are dedicated to document the need for adequate funding.
2. In-house expertise needed. A further 5 paragraphs are dedicated to this need which include citing quotes from the Krever report for independent science and ends by stating that CHA urges Health Canada to reinstate the calibre of in-house science necessary to remain current with the development in technology and to maintain control over the integrity and quality of that science.

16 - Canadian Health Food Association presents a philosophical commentary which states there needs to be a clear delineation of what is meant by the "public good" and the "private good". Evaluation of drugs which save lives etc.. seems to be for the "public good" and therefore NOT (my upper case) consistent with the philosophy of paying only for services which benefit the "private good". Annual inspections and renewal of drug and manufacturing licences are deemed to be in the "private good" but the review of drugs seems to fall within the domain of the "public good."

17 - National Health Coalition – no direct response.

18 - Canadian Hemophilia Society – no direct response.

21 - Canadian Pharmacists Association has no concerns over cost recovery having been participated in consultations on the subject. The Association is aware of the questions being raised and suggests that in order to address those concerns, it may be important to educate the public more about the scientific basis on which the approval process is based.

23 - Canadian Public Health Association:

- If drug review is to protect the public from untested or unsafe drug products, then fees seem inappropriate because the client is the Canadian public not industry;
- If the drug approval process is something other than protecting the public but to provide industry with a "Canadian Stamp of Approval" for its products then the industry should pay fees commensurate with the profits realized from the sale of its product;

- The Canadian public should expect to understand the function of the drug review process, and should agree with the programme, as well as its policies and processes.

25 - Canadians for Health Research supports cost recovery as a practice carried out in other countries and believes that cost recovery does not influence the drug review process:
- CHR believes the public does not support cost recovery due to assertions made by former and current HPB employees. Health Canada has not effectively addressed these allegations and CHR does not believe that public concerns can be alleviated;
- CHR suggests that the issue be thoroughly reviewed, particularly from an economic perspective.

28 - Consumers' Association of Canada does not support cost recovery and states that consumer confidence with respect to HPB's credibility as a body that is mandated to protect the health of the public has been weakened. Examples cited include: the tainted blood scandal, media stories that document undue pressure for approval – such as the management of the dis/approval of rBST – have further underscored the department's failure to live up to its mandate:
- Full funding and restoration of in-house research capacities are key to regaining public confidence;
- Any fees collected should be returned to general revenue and should never be seen as a source of departmental revenues or an indicator of effective performance;
- Management at the most senior level must truly believe that it is the public , not the industry, who are the "clients" and that they do not share the industry concept of risk-management as the foundation for drug approval;
- There may be an opportunity to create a fund, through a new industry tax, that would support compensation for unanticipated problems with drugs, products and devices. This tax could also support independent mechanisms (i.e. without the participation of those who would profit, directly or indirectly, from the activities) to establish long-term monitoring, and to develop consumer information, including clear and comprehensible inserts.

30 d - FDA: Concerning unfair influence of the drug review process due to charging fees; this is surely an area which deserves to be watched. However, FDA experience so far has not revealed unfair influence.

31 - GPIM – the Quebec-based group of pharmaceutical manufacturers believes that cost recovery can only influence the efficient timeliness of the evaluation process not the actual approval. However, they note that the public perceptions of cost recovery have been poorly managed.

32 - Heart and Stroke Foundation of Canada comments on principles: question 6.

33 - Medical Reform Group does not support cost recovery:

- If industry pays the costs then it will be perceived as having undue influence over the process – whether or not that is the case;
- The issue of user fees itself is something that needs to be examined closely;
- Medical Reform Group concludes that "the approval system is there to benefit the public and as a reflection of that principle should be funded as a public service through the tax system."

36 - Nonprescription Drug Manufacturers Association is concerned about a public perception that paying fees influences the process and outcome of the review of drug submissions:

- Gives reasons for concluding that the process is not influenced by industry through cost recovery but that cost recovery simply adds unnecessary cost to the marketplace;
- Cites the US experience where fees are paid directly for drug reviews permitting increase in resources for the drug review process whereas in Canada cost recovery replaces government appropriations without a net increase in resources;
- Suggests any fees paid in Canada be in addition to sufficient funding to increase resources which would lead to shorter review times and the new therapies being made to Canadian in a more timely manner.

38 - The Parkinson Foundation of Canada comments: There is too great a potential for misunderstanding and misinterpretation in the charging of fees for drug review. The perception could be that the process would unjustly favour the group that expended the greatest fee. Any costs should be standardized and equitable; the review process and approvals unencumbered.

40 - Patented Medicines Prices Review Board : No concerns.

41 - Pharmaceutical Manufacturers Association of Canada strongly takes exception to the allegations in the (your) question regarding fees for Drug Submission Review:

- There is no evidence that any element of cost recovery has led to undue influence being brought to bear on decision-makers;
- The effect of cost recovery has been diminished performance by TPP;
- PMAC is not pre-disposed to defend or to oppose the imposition of fees;
- PMAC is participating in the mandated Cost Recovery Phase IV review of the current policy and its application and will continue in good spirit to make the system work;
- Major concern of PMAC member companies is the unsubstantiated allegations of undue influence which are left unchallenged and the fact the PMAC companies have to justify cost recovery as the TPP themselves appear unable to do so.

42 - Provincial Ministries of Health (Nova Scotia) states that Health Canada must provide appropriate **base funding** to allow high quality scientific review of new drugs:

- Base funding must be in place to ensure that an adequate number of researchers are in place for an adequate period of time with access to adequate resources to complete the reviews;
- Not opposed to charging fees though 100% cost recovery would be unrealistic;
- Industry must know what to expect for their money;
- Some clearly stated industry expectation may need to be developed to ensure the drug review process cannot be unfairly influenced.

45 a - Dr. Holbrook states that charging of fees for drug review is a major concern.. If the majority of funding for the drug approval process comes from industry, a perception of bias is unavoidable. This could be best countered by an open, transparent and rigorous process with external scrutiny and involvement:

- She also believes that taxpayers should not expect the drug industry to entirely fund the drug approval process, but it may be reasonable to require the industry to pay a substantial fee for access to a market which returns to them significant profits. Furthermore, it is the opinion of many that the fee structure should build in penalties for companies submitting disorganized, incomplete or at worst deceptive packages.

45 b - Dr. Noni MacDonald does indeed believe charging fees can influence the drug review process. Companies benefit from products reviewed and accepted, make money on the product and pay taxes. In case of orphaned drugs, paying an additional amount makes the "pay to play" process less attractive to the company. Somewhere in this murky pool of need for cost recovery versus the rights of society to speedily have good drugs approved, we need to find a balance.

45 c - Dr. John Gill's opinion – supports cost recovery, and in his opinion, user-fees do not create a conflict of interest.

47 - Merck-Frosst accepts the concept of charging fees which has been adopted in other jurisdictions, but does not believe payment of fees influences the drug review process, and furthermore suggests that an appropriate balance of support provided by government and the pharmaceutical industry can ensure the independence of the Regulatory Agency:

- Merck-Frosst has concerns that fees for drug review have not all been devoted to support activities related to the drug review process. Levying of fees has not translated into an acceleration nor improvement of the drug review process. No changes in regulations have yet been made to institute continuous quality assessment of the review process, to reduce the fee schedule, or to formally link fee payment with improved time frames for completion of services;
- Merck-Frosst concurs with the analysis of user fees conducted by the Business Coalition on Cost Recovery, a copy of which is attached to the response letter.

48 – Canadian Association for Population Therapeutics has no objection to user fees for the drug review process. However, the fees should be used to enhance the process, not just to provide extra funds for general revenue. Furthermore, the entire process needs to be open and published and the affected industries should be guaranteed they receive appropriate value for that which they have paid.

49 - Multiple Sclerosis Society of Canada is unable to comment.

56 - Federal/Provincial/Territorial Pharmaceutical Issues Committee does not respond directly to the six questions. Please note that this response is signed by two persons one of whom responded to most of the questions – refer to Provincial Ministries of Health (Nova Scotia), number 42 above.

Question 6

What principles should guide the drug review process?

7 - CMA has long been on record as supporting the Gagnon Report:

- important aspects of Gagnon Report are yet to be implemented;
- deficiency in Post Marketing Surveillance (PMS); it was formerly thought that PMS would encompass the safety aspects of new drugs. This has not been the case. A solution would be to direct this aspect back to the industries and have them take responsibility for obtaining this information;
- PMS should focus on both effectiveness and adverse reactions;
- CMA attached a copy of its letter of June 8, 1993 to the DM Health Canada and its three comments on the Gagnon Report are:
  1) CMA agrees with the general direction of the report and, in particular, directs attention to the emphasis placed by Dr. Gagnon on PMS
  2) MA wishes to stress the need for additional activity in PMS programs in Canada, particularly if other recommended measures reducing pre-market scrutiny of drugs are adopted, and
  3) CMA is willing to assist in the implementation of improved PMS and to assist in the coordination of any new programs with existing systems of PMS in Canada.

9 - Canadian Treatment Advocates Council:

- Canadians should have timely access to medicines proven to be safe and effective;
- Process of reviewing new drug submission should be more open – one that is both transparent and accountable;
- The drug approval process should include all active post approval surveillance of drugs incorporating the following components:
  1) Ongoing, systematic collection, analysis and interpretation of adverse effects, toxicity, drug interactions, and the long-term effectiveness of drugs following market approval
  2) The use of this data for decisions about a drug's safety and clinical indications
  3) Timely dissemination of the data to all stakeholders
  4) Prescribed reporting systems
  5) The involvement of the community, persons living with HIV, researchers, the pharmaceutical industry and health care providers in all aspects of the above components
- The equation of risk versus benefit should be considered in a way that achieves an appropriate balance and is reflective of Canadian values.

  Canadian Treatment Advocates Council also appended two reports: a 36 page report, plus appendices A to F, entitled "Timeliness and Transparency" - Assessing the Review of Process for HIV Drugs", November 1998. and a second, six page report entitled "Consultation Workshop on Approval of New Drugs in Canada", August 12, 1998.

10 - The Canadian Cancer Society has three recommendations:

- First, that HPB clearly delineate its mandate. Is HPB mandated to find benefit in addition to safety in order to approve drugs or devices? If it does not take on the function of assessing benefit, does it link to the organization that does? The Canadian Cancer Society affirms the position that a single federal body should oversee health protection of drugs and devices for the public good and that this not be left to other levels of government;
- Second, that the HPB process be more transparent. This will allow more direct public input into the review process and may allow information regarding the worthwhileness of drugs or devices to be more widely available;
- Third, that there be an ombudsman function undertaken by HPB. Currently, the only means by which a drug or device can be reviewed by HPB is if a submission is put forward by industry. It could happen there is a new treatment which is widely believed to be a significant advance but is delayed because a multinational company is busy trying to get their product approved in another country; an ombudsman office could be a means by which a direct appeal from the public could be made to HPB.

11 - Canadian Diabetes Association believes the process should be driven by the principles of:

- Responsiveness – new treatments that may positively affect the health of Canadians;
- Accessibility – ensure that Canadians have timely access to new therapies as others do world wide;
- Risk-Benefit-Management – for new therapies where none presently exist, an additional degree of risk may be acceptable.

12 - Canadian AIDS Society believes that the primary mandate of HPB and the drug review process should be the implementation and monitoring of safe and effective medications into (in) Canada in a timely transparent manner.

The Society also comments on its concerns about the availability, diminished effectiveness, and side effects of anti-viral and other drugs used singly or in combination to treat AIDS/HIV patients.

Canadian AIDS Society also submitted three documents:

- Position Statement: Reform of the Drug Review Process at the Health Protection Branch, September 1998 and background to the position statement;
- Advocacy Update: Reform of the Drug Review Process at the Health Protection Branch, September 1998. Issues include: efficiency, transparency and accountability, resources and next steps to be taken;
- A 36 page report, "Timeliness and Transparency" - Assessing the Review of Process for HIV Drugs", November 1998 plus appendices A to F. This is the same report as submitted by the Canadian Treatment Advocates Council, number 9 above.

13 - Canadian Drug Manufacturers Association believes the principles should include:

- Harmonization with respect to standards and approvability criteria;
- In cases where harmonization is not achievable, increased effectiveness in application of resources should be exercised;
- Application of sound business practices in operation of cost-neutral centres;
- Accountability to stakeholders and submission sponsors for review quality and timeliness;
- Transparency on policy development and applications;
- Sound scientific reasoning should be employed rather than blind adherence to Guidelines in the review process when they are in conflict.

Canadian Drug Manufacturers Association also attached two appendices: These relate to safety and efficacy discussion points, chemistry and manufacturing discussion points and screening discussion points as well as three documented graphs: "hold times" Since End of Screening to Start of Chemistry and Manufacturing Review Since January 1, 1998, a second graph "hold times" Since End of Screening to the Start of Safety and Efficacy Review Since January 1, 1998. The third graph shows Screening Submissions Filed and Screened Since January 1, 1998.

14 - Canadian Society of Hospital Pharmacists suggests the following principles:

- Transparency to all stakeholders;
- Freedom from political interference;
- Equity of access to the process for all drug submissions;
- Enhanced consumer safety through minimized risk;
- Maintaining currency in the science and clinical aspects of drugs.

15 - Canadian Healthcare Association believes a number of principles should be included and these are summarized in two paragraphs:

- The overarching principle of HPB should be protecting the safety of Canadians. Specifically, this means that maintaining and improving the health of Canadians will take precedence over industrial, economic and trade issues;
- The principles guiding the drug review process should promote the use of science-based information in decision-making; ensure a fair, equitable and transparent approach; and address the issues of accountability and liability.

16 - Canadian Health Food Association: honesty, integrity, transparency and efficiency with the ultimate goal of providing the best and safest drugs to the Canadian public within the most reasonable timeframe possible.

17 - National Health Coalition – no direct response.

18 – Canadian Hemophilia Society – no direct response. Summary of comments and concerns are as follows:

- Lack of transparency with respect to drug submissions, drug safety and efficacy;
- Decision that a product manufactured from blood of a donor with CJD is safe without being able and/or willing to share data with "us";
- Supports several (unspecified) Krever recommendations, but emphasizes a "safety first" principle;
- A copy of correspondence with HPB February, March and April 1999 concerning the Utah CJD blood donor issue is also appended.

21 - Canadian Pharmacists Association believes that the principles to underlie the drug approval process should be:

- Safety, fairness, efficiency, cost-effectiveness, transparency and accountability.

23 - Canadian Public Health Association comments that the principles in the TPP document "Strategic Framework for 1998 – 2001" appear to be comprehensive and logical. Perhaps a review of the stated principles would be constructive for future planning and operations.

25 - Canadians for Health Research comments as follows:

- The responsibility of HPB is to ensure that a product is safe and effective, with these judgements based on purely science;
- Decisions regarding the use of a product should be left to the marketplace.

28 - Consumers' Association of Canada comments:

- The drug review process should be guided by principles of timeliness, efficiency and effectiveness but the emphasis must be on medical need and safety;
- The process must become an open and transparent system with early opportunity for public input – with supports in place to ensure public participation;
- Funding of the process should come from general revenues where licensed fees should be deposited; no links between licence fee and approval – whether real or perceived – should be allowed;
- Process must be free from financial and political pressures in order to be objective and to act in the best interests of the public;
- Decision-making must be based on science.

30 d - FDA:

- Scientific soundness, integrity and consistency are essential to a successful review;
- The foremost conclusion, last year, of an FDA external review committee is as follows:

  > It is the consensus of the Review Committee that for our industry to receive prompt and appropriate regulatory reviews, as well as for the ability of the regulatory agency to respond to urgent needs, it is of utmost importance that the scientists have research capabilities at the cutting edge that allows them not only to understand the

rapidly expanding methodologies to evaluate vaccines and biologics, but also that scientist/reviewers can interact with their colleagues in industry on a knowledgeable and scientific and technological basis so that appropriate recommendations can be made.

- FDA is implementing that recommendation.

31 - GPIM – the Quebec-based group of pharmaceutical manufacturers believes the principles included: (note – this is my interpretation which may not be accurate.)

- Analysis of known risks be based on scientific data;
- Often too much interpretation reflects a purely Canadian science (?);
- Transparency of the process at all steps;
- Fairness to the public and the industry;
- A reduction of TPP budget could signal that the government attaches little importance to the work of the TPP, including the drug review process.

32 - Heart and Stroke Foundation of Canada cites the example: Recently HPB approved tPA for use in select cases of acute stroke. The Foundation had been following the process closely. The drug approval process appears to be highly secretive and the Foundation's first knowledge of the approval was a media call and hearing a press conference by the manufacturer announcing its launch. The Foundation would like to have been notified in advance of the release in order to hold their own press conference highlighting for the public the early signs of stroke, how to enter the emergency system immediately (within a the three-hour time frame window) and how the health system must reorganize to meet the new realities of a drug requiring, prior to use, a CAT scan and excellent neurological services. The Heart and Stroke Foundation is a trusted and authoritative voice to the public and their message could have been important in reducing time delays.

Using this example, the Foundation puts forth the following principles for consideration:

1) Canada must maintain an evidence-based drug approval process. This should be based on safety, efficacy and quality;
2) The most significant criteria for assessing and improving therapeutic products should be the health and safety of Canadians;
3) Every effort should be made to expedite the drug approval process. One way may be to work collaboratively with the US as the borders between our countries become more porous. A joint US/Canada review process and simultaneous release of drugs may be beneficial to Canadians in terms of timely access to new therapeutic products;
4) The process of drug review should have greater transparency and the external review bodies should be known to the public;
5) Post-marketing surveillance is required to ensure that once a drug is approved and moved from a randomized control trial environment to the "real world" its effectiveness is monitored and a system is in place that allows for drug recall if necessary;

6) The funding of the drug review process is a legitimate expense for industry and this in no way should, or would, influence the process. This should not be a revenue generating function for government, but cover all legitimate costs of reviewing drugs;
7) Consideration should be given to a greater inclusiveness of the constituency in the actual drug review process (e.g. internally at Health Canada, the Laboratory Centre for Disease Control, Statistics Canada etc., and externally not-for-profit organizations, professional associations and potentially members of the public).

33 - Medical Reform Group considers the principles of drug review process to be incorporated in the answers to the first five questions:
1) An emphasis on medical need in approving new drugs;
2) A system that maximizes the risk/benefit ratio of drugs;
3) A commitment to transparency and meaningful public input;
4) Funding the system as a public service through tax dollars.

36 - Nonprescription Drug Manufacturers Association believes that to have a process which is efficient and effective the following principles should guide the process:
- Timely review of drugs leading to improved health and quality of life of the Canadian public. Drug review times must be realistic and internationally competitive;
- A science-based approach to the review process;
- Application of risk/benefit assessment and management. Products of equivalent risk must be regulated in a consistent manner;
- Fairness and consistency in the review process;
- Open dialogue between industry and Health Canada during the review process;
- Transparency in the drug review process through a publication of standards of evidence for review.

38 - The Parkinson Foundation of Canada states that those principles currently guiding the drug review process (e.g. safety) in Canada require little criticism:
- Perhaps HPB should strive to avail itself of the wealth of medical expertise that exists in this country, to assist and guide them in their review and decision-making;
- The Foundation cites an example of the drug Tolcapone/ Tasmar where none of the internationally renowned Movement Disorder neurologists practising in Canada was consulted prior to HPB's decision to discontinue the prescription use of this anti-Parkinsons agent. Two of these doctors received the Order of Canada for their contribution to the specialty (Dr. Ali Rajput and Dr. Donald Calne) and another is a world-renowned researcher and clinician – Dr. Anthony Lang.

40 - Patented Medicines Prices Review Board suggests:
- Decisions to approve new drugs should continue to be based on good, scientific evidence;

- The review process should be more transparent; information concerning the rationale for recommending approval and the evidence on which the approval was based should be publically (publicly) available;
- The review process should be efficient; duplication of effort should be minimized whenever possible;
- The process should be publicly accountable both in terms of the quality and timeliness of the review; more information concerning the review process is required for this to happen.

41 - Pharmaceutical Manufacturers Association of Canada cites the most important principles as being:

- Protection of the public by the identification, evaluation and management of the health benefits and risks associated with drugs; and
- That decisions are made on the best available science.

MAC comments that additional principles that guide the drug review process are already in place within the mission statement of TPP. The principles are the product of many reviews of mission and mandates of TPP over the last 13 years. They should be adhered to particularly as related to concepts of timeliness. There is also an expanding notion that TPP – a science, fact-based body – should, in the review of submissions – begin to apply principles of cost effectiveness and comparative therapeutic assessment to products which it is charged with evaluating for safety and efficacy. This area is rightly the purview of the ultimate provider once products are approved. This is not an appropriate role of TPP or HPB.

42 - Provincial Ministries of Health (Nova Scotia) have no comments for question 6.

45 a - Dr. Holbrook recommends scientific vigor, transparency and primary attention to good health.

45 b - Dr. Noni MacDonald feels that the drug review process should include:

1) Emphasis on the quality of the scientific review;
2) Sufficient time to do a high quality assessment;
3) Arm's length from any conflict of interest in the review process;
4) Openness of the review and transparency of any outcome;
5) Public access to easily interpretable drug safety information;
6) A mandatory re-review process should serious post marketing adverse events occur;
7) A recognition of the uniqueness of the health care delivery system in Canada and the responsibility for the greater good of the population in any decision making;
8) A balance between needs for cost recovery against the needs of society for the product (there may be special categories where fee payment may not be the best route);
9) More emphasis in the requirement for new product submission (so) that the drug needs of infants and children, adult women, and the elderly are addressed appropriately. (Too much

drug safety and efficacy info has been focussed on young adult males hence there is little or no information on how the drug could be used in these other populations.);

10) Re breadth and depth of expertise in HPB, we very much need, as Canadians, to ensure that more senior bureaucrats have sufficient medical expertise to thoughtfully steer us through conflicting areas. Too often the technical expertise has been too low down in the decision making chain. "This worries me immensely."

45 c - Dr. John Gill comments that the review process should look for safe and effective products. There should be an ability to expedite reviews and to approve certain new agents with a notice of compliance with conditions (NOCC) and then mandate by law a follow up for NOCC products released early in their development cycle into the Canadian marketplace.

47 - Merck-Frosst response:

- Regulations should ensure that drugs approved for use in Canada are safe, effective and of highest quality;
- Canadian legislation should ensure that patients have rapid access to new and innovative therapeutic products and break thorough developments in medical research;
- Review of submissions and acceptance of therapeutic products should be based on scientific assessment of benefits to patients taking into consideration the relative risks to be incurred;
- The review and approval process of drugs should be:
  1) Based on sound scientific evidence;
  2) Transparent while safeguarding proprietary information;
  3) Easily understood by the public in general;
  4) Fair and equitable to the parties involved;

More fruitful, flexible collaboration between industry, academia and the regulators would allow learning in the rapidly developing areas of therapeutics, as well as in the more tangible business of new drug development

Merck-Frosst also appends two papers and several graphs illustrating the concept of timeliness. The titles of the papers are:

Drug Review In Canada: A Comparison with Australia, Sweden, the United Kingdom, and the United States, Rawson, Nigel S.B. et al, Drug Information Journal, Vol 32 pp1133-1144, 1998, and User Fees: Where Does the Buck Stop – A Study of Cost Recovery, January 1999 available from the Alliance of Manufacturers and Exporters (613) 238-8888 ext. 236 or Web site www.the-alliance.org.

48 - Canadian Association for Population Therapeutics comments as follows:

- The drug review process should be guided by the principles of continuous assessment of the risk-benefit balance of products being reviewed. This should include definable criteria for assessing risks, benefits and quality of medicinal products;
- The goal should be the best care at the best cost or, alternatively, maximizing benefits and minimizing risks at best cost;
- Presently in Canada, there is confusion about the process of drug evaluation, drug approval and drug listings (provincial formularies) that requires clarification by Health Canada by way of a public statement on its health care policy. This should include Health Canada's commitment to sound public health principles and its role as guardian thereof.

49 - Multiple Sclerosis Society of Canada states guiding principles should be:

- Allowing Canadians access to proven drug treatments in a period of time that is equal to that of nations with similar levels of economic development and health systems;
- Safety of the review process to protect the health of Canadians;
- Transparency of the process at all steps along the way;
- Easy public access to information about drug safety and efficacy of approved drugs.

65 - Federal/Provincial/Territorial Pharmaceutical Issues Committee does not respond directly to the six questions. Please note that this response is signed by two persons one of whom responded to most of the questions with the exception of this question – refer to Provincial Ministries of Health (Nova Scotia), number 42 above.

Russ Graham
June 25, 1999

COMMITTEE ON DRUG REVIEW PROCESS
Report
Observations and Consultations
Washington, DC
July 19 - 21, 1999

1. Background

1.1 The Committee was struck by agreement of the Science Advisory Board at its meeting of March, 1999, and is chaired by Doug Elliott. Members include Russ Graham, Jean Jones, Leslie Millin and Karen Semchuk, with Bernard Schwetz as an adviser. Terms of reference are as attached.

1.2 The Committee agreed early in its work to examine as soon as feasible the public hearing process used in the United States by the Food and Drug Administration, since this is frequently cited in Canada as an alternative to the process used by the Health Protection Branch of Health Canada. With the generous assistance of Dr. Schwetz a program was arranged combining direct observation of public hearings with interviews with key FDA staff.

1.3 Dr. Semchuk was unable to participate, but other members participated in all meetings and attended the public hearings. Dr. Schwetz attended most meetings.

2. Public Hearings

2.1 The public hearing process is perhaps the most striking difference between the Canadian and the U.S. drug review process. In the United States, in principle, each New Drug Application is potentially subject to a review in public wherein the applicant ("Sponsor", in FDA terminology) defends its application; an advisory committee appointed by the FDA questions the applicant, sometimes with the help of external experts; and the general public has the opportunity to present facts or arguments deemed relevant to the application. In practice, the advisory committee process is invoked at the discretion of FDA management when it is deemed appropriate. Sometimes the committee votes; sometimes FDA staff simply take official notice of the proceedings. In any case, final responsibility for disposition of the application rests with the FDA. In Canada, in contrast, the review process is internal to HPB, with high levels of confidentiality attached to the information supplied in support of the application.

2.2 We observed two public hearings. Both were held in a suburban hotel in the Washington area, some distance from the city centre. The first, on July 20, was a joint meeting of the Nonprescription Drugs and Arthritis Advisory Committees; the second, on July 21, was a meeting of the Arthritis Advisory Committee alone. These hearings follow a fairly standard format: presentation by FDA staff; presentation by the applicant; time for public questions or comment; wrap-up discussion among committee members. We were impressed in particular by the amount of detailed information that was placed upon the public record, not only by FDA staff but by the applicant companies. In the first hearing, six FDA staff were allotted a total of 75 minutes to review specific aspects of the application. The applicant, Merck & Co., had an equal amount of time to speak in support of its application. Not only did the applicant provide voluminous, detailed information in its chief presentation, it provided prompt and exact responses to the 42 questions posed by advisory committee members. Only one member of the public spoke, a representative of an advocacy group, with whom we later had an informal consultation. Interestingly, this intervener made the argument that the fact that Canada had authorized use of a certain product--a point made by the applicant company--should be disregarded, because the secrecy of the Canadian process made it impossible to judge the validity of the outcome. The hearing on the next day was rather similar. Both hearings were recorded on video by three separate companies which provide cassettes to the public on a commercial basis. At least one of these companies was broadcasting the hearing live on the Internet--a striking contrast with the Canadian system.

2.3 We met informally with Larry Sasish of the advocacy group Public Citizen. This group likes the public hearing system--indeed, there seems to be unanimity on this. It has reservations about user fees, more or less on principle; but its concerns are much greater that senators and representatives may have undue influence on the FDA, and that this may be affected in turn by campaign contributions from manufacturers.

2.4 In general, we were impressed by the public hearings. Some of us have various reservations about the process, and we have no information at this time on the typical cost of such a hearing; but the important point is that within the FDA context, drug companies are expected to routinely make a great deal of information available, and they do this without apparent qualm. Indeed, we were struck by the fact that the public hearing process seems accepted without question or challenge by all parties.

3. Interviews

3.1.1 We met first with Dr. Murray Lumpkin, deputy director, Center for Drug Evaluation and Research. Dr. Lumpkin supplied us with much detailed information in writing, but also gave extensive and very useful commentary. In particular, he described the background to and the implementation of the *Prescription Drug User Fee Act*, originally passed in 1992 and confirmed in modified form in

1997. He clearly considers this to be a success. PDUFA is an unusual program, not least in that the fees paid do not flow through the U.S. Treasury but through a private bank, and that the Congressional appropriation is not allowed to go below the level set in 1992; further, the fees are rolled over from fiscal year to fiscal year. Dr. Lumpkin notes that the name-brand prescription drug industry is happy with PDUFA and co-operates with it readily, having been actively involved with its creation. The companies manufacturing generic drugs chose not to be involved, and are not covered by PDUFA. A consequence is that there are now in effect two types of operation within FDA: those under PDUFA, which enjoy extra resources and special flexibility in using them; and those which are restricted to Congressional appropriations and Treasury rules. Dr. Lumpkin told us that user fees have had no deleterious effect in terms of the public interest. We noted that part of the reason why the name-brand drug companies are pleased with PDUFA is that they were promised certain improvements in the process--notably, timeliness--as a *quid pro quo*; and these have in fact been delivered. An area of concern, however, is post-approval surveillance.

3.1.2 Dr. Lumpkin described the work of the advisory committees, which again he clearly considers a successful system. Most committee members are chosen for their professional qualifications, but each committee has a consumer representative selected through FDA's Office for Consumer Affairs, and some also have a patients' representative selected through the Office of Special Health Issues. Committee members are designated as "special government employees", and paid a nominal daily amount over and above their expenses, thus binding them to government rules on confidentiality and conflict of interest. The advisory committees are in no way unique to FDA, but rather reflect a consistent policy of the U.S. government, and are governed by the *Federal Advisory Committees Act*. As an interesting coincidence, at the first public hearing we attended the extensive briefing notes supplied to the committee were for the first time simultaneously released to the public, an important extension of practice as the result of a recent court order pursuant to the *Act*.

3.1.3 We were interested to be informed that Dr. Lumpkin's staff have a monthly video conference with the staff of Health Canada's Therapeutic Products Program. Dr. Lumpkin is an enthusiastic supporter of international harmonization.

3.2 We met with Ms. Pat Kuntze, Acting Associate Commissioner for Consumer Affairs. She described the work of the Office, which has been active for some 20 years. It supports the activities of the consumer advocacy movement, primarily through the Consumer Consortium, a group of about a dozen organizations. As noted above, it manages the selection process for consumer representatives on advisory committees, and provides support and orientation for them. Formerly, the OCA provided financial support for some consumer groups to prepare themselves for participation in public hearings; but this has ceased due to a court ruling.

3.3.1 We met with Rear Admiral Marlene E. Haffner, Director of the Office of Orphan Products Development and her staff. She briefed us on the background and work of the Office, which originated in legislation passed in 1983. Essentially, its purpose is to bring to market therapeutic products for which demand is too small to attract the interest of major manufacturers. This is done through a complex of incentives: marketing exclusivity; tax credits; protocol assistance; and research grants.

3.3.2 Rear Admiral Haffner stressed the strong desire of her Office to enter into co-operative projects with Canada. OOPD has already undertaken a number of projects involving non-American researchers. One reason for seeking Canadian projects arises from differences between the American and Canadian medical systems: a major element in the costs associated with American projects is patient care, which private insurance companies in the USA will not cover, but which are automatically covered under Canada's universal system. This allows more of the grant resources to be applied specifically to research.

3.3.3 She noted that although Canada has had an interest in orphan products, she has no continuing contact with her Canadian counterparts.

3.4 1 We met with Theresa Toigo of the Office of Special Health Issues and her staff. This Office appears to be an offspring of the Office for Consumer Affairs, and responds principally to the needs of people afflicted by cancer or AIDS. It is responsible for recruiting and training patients' representatives for advisory committees dealing with these conditions, and more generally for acting as a liaison between the FDA and the communities of cancer and AIDS sufferers.

3.4.2 OSHI has a small but remarkably enthusiastic staff. We were impressed with the quality of its publications.

4. Conclusions

4.1 Our overall immediate conclusion is that this visit was informative and thought-provoking, and has contributed substantially to the work of the Committee. While the American drug review process is not entirely as open as often suggested, there is clearly a very different dynamic at work than in Canada among the drug companies, the regulator, and the public.

4.2 As our nearest neighbor, largest trading partner and major source of therapeutic products, the United States was the logical place to examine first. The extent and diversity of what the Committee found is an encouragement to move to consideration of other jurisdictions.

August 21, 1999

COMMITTEE ON DRUG REVIEW PROCESS
Report
Observations and Consultations
London, United Kingdom
October 24 - 28, 1999

1. Background

1.1 After the Committee's examination of the drug review process used in the United States through the Food and Drug Administration, it was agreed to essay a comparable direct contact with appropriate officials of the Medicines Control Agency of the United Kingdom and the European Agency for the Evaluation of Medicinal Products. Both are headquartered in London.

1.2 Initial efforts to fix a meeting for the Committee with the head of MCA were not possible in the available time frame. However, it was agreed that Leslie Millin on behalf of the Committee would undertake consultations with these agencies at an intermediate level, as well as gathering whatever useful background might be possible in a brief visit.

1.3 The purpose of this document is to report on this activity.

2. Medicines Control Agency

2.1 Millin met with Shaun Delaney and Leslie Whitbread. Mr Delaney is Scientific Support Manager to the MCA Chief Executive Officer. Mr. Whitbread is Secretary to the Committee on the Safety of Medicines.

2.2 Both stressed that a primary feature of the drug review process as conducted by the MCA is confidentiality. "While the process is in train, nobody but us sees it." Also: "The bottom line is secrecy." This is mandated by legislation, and is scrupulously observed. However, the UK government is committed to introduce legislation on freedom of information, and the MCA has given thought as to possible implications for the drug review process. Until the actual legislation is tabled, it is impossible to predict what requirements may be made. Edited summary minutes of expert advisory committees are being placed on the Internet and are updated after a decision is made and gazetted on any new drug application. The MCA is aware of growing public pressure for more information on the drug review process.

2.3 The MCA retains a staff of some 540, divided approximately 50:50 between professional and administrative staff. It works through standing committees of outside experts. It maintains no internal scientific laboratories, working instead through external laboratories through a service level agreement system. These external laboratories have been fully audited, and are subject to technical and confidentiality agreements.

2.4 Average assessment time for an NDA is 30 to 45 days. However, the MCA works closely with manufacturers well before any formal application is made, ensuring that swift consideration is typical. "The aim is to have *partnerships* with industry."

2.5 When the MCA was created, its two immediate tasks were to clear the backlog of outstanding NDAs and to achieve financial self-sufficiency. Completing these tasks took about three years. The MCA is now completely financed through user fees, and has managed to reduce these fees by about 35 per cent over the agency's life. It operates according to annual business plans approved by the Secretary of State for Health.

2.6 Such is its success that the MCA now competes with other European Union member states for NDAs. Mutual recognition agreements mean that UK approval affords ready access to other EU jurisdictions.

2.7 Post-approval monitoring is "a growing area". The MCA is bound under legislation to make available to industry adverse drug reaction reports notified by health professionals within14 days, and has the capacity to do this electronically.

2.8 International harmonization, working with and within ICH guidelines, was described as "a commitment".

2.9 The MCA supports the EU initiative on Orphan Products. (See appendix H)

2.10 The MCA has continuing contacts with Health Canada's TPP.

3. European Agency for the Evaluation of Medicinal Products

3.1 Millin met with Dr. Patrick le Courtois, Head of Sector, Human Medicines Evaluation Unit; and Antoine Cuvillier, Directorate Administrator.

3.2 The EMEA is financed through user fees and appropriations from the European Parliament. User fees typically account for 60 - 75 per cent of revenues; a 75:25 ratio is considered ideal.

The purpose behind appropriations is to ensure that certain activities such as special research projects can be funded even though they are not immediately related to an NDA.

3.3 User fees are widely employed throughout member states of the EU, generally successfully. However, it was noted that such success generally depends on the regulatory agencies having *special agency* status--where regulation was done through line departments, a problem invariably arose because user fees went into consolidated revenue rather than being specifically earmarked for evaluation activities.

3.4 Basic review of an NDA takes place within 210 days, and this has never been exceeded. However, in certain circumstances the clock can be stopped. For a first report, the target is 70 days. A standardized template for documents assists in ensuring that an NDA's data are complete upon receipt. Mutual recognition status across the EU is obtainable upon application by the manufacturer (see 2.6 above) and typically takes 90 days. Identical information must be supplied by the manufacturer to all EU member states to obtain mutual recognition.

3.5 International harmonization is in a sense a *raison d'etre* of the EMEA, and it is active in such venues as the International Committee on Harmonization. Further, it has agreements with various countries of central and eastern Europe, as well as Latin American countries such as Brazil and Argentina.

3.6 There is at present no orphan product program, but the necessary legislation is at the second reading stage and it is anticipated that it will come into force by next summer. The proposed program is clearly influenced by the US and Japanese experiences, and reflects a similar blend of incentives. The proposed program is described in detail in the document attached to this report.

4. General observations

4.1 Discussions with colleagues elicited several observations of interest, and these were supplemented by desk research.

4.2 One is that the UK system of clinical trials of new products is controversial. A 10-year audit of such trials found that the procedures to decide the safety and effectiveness of new products were flawed to the point of endangering the health of those taking part. In a sample of 226 trials, significant under-reporting of side effects was found in about 30 per cent. Insufficient proof of drugs being stored at the correct temperature was found in 55 per cent, and 43 per cent of patients were found not to have been given clear instructions about the use of the drug being

tested. There have also been reports that international manufacturers have taken to testing their products in the UK in recent years because the trials they want would not be permitted in other jurisdictions, notably the United States. These allegations are, of course, contested.

4.3 Another general observation is that the special agency status of the MCA, while it has worked very well in terms of its mandate, carries certain penalties. Its work methods are such as not to attract or retain the best scientific talent, since it has no laboratories and its staff are in any case governed by strict rules of confidentiality. Further, the special agency status makes for a degree of organizational isolation--staff cannot readily move around from department to department, as was formerly the case, so the opportunity for intellectual cross-pollenation is correspondingly reduced.

4.4 The general climate of anti-scientism throughout western Europe is striking. At present, the issue of genetically modified foods and other substances is the major condensation point. A major UK retail chain now posts prominent signs saying that none of the foodstuffs on sale has been genetically modified. Scientific tests on genetically modified plants have been vandalized. With the growing globalization of information flow, we can anticipate that similar anti-scientific activities may well manifest themselves in Canada before long, if indeed they are not already with us.

Leslie Millin
November 10, 1999

Appendix D

COMMITTEE ON DRUG REVIEW PROCESS

Science Advisory Board, Health Protection Branch
INTERIM REPORT

October, 1999

1. Background

1.1 The Committee was struck by agreement of the Science Advisory Board at its meeting of March, 1999 and is chaired by Doug Elliott. Members include Russ Graham, Jean Jones, Leslie Millin and Karen Semchuk, with Bernard Schwetz as an adviser. Terms of Reference are appended as Annex A.

1.2 Early in its work, the Committee agreed to submit its Final Report at the SAB meeting scheduled for November, 1999 with an Interim Report to be available for the September meeting. This Interim Report is intended to identify issues and provide some commentary as a basis for discussion and for future work of the Committee, but not to offer recommendations—these will be contained in the Final Report.

1.3 Observations made in this Interim Report, unless otherwise attributed, are based on the consensus of Committee members, drawn from their consultations and desk research. Citations are not provided. The Final Report will be appropriately footnoted.

2. Work to Date

2.1 The Committee to date has:
- Reviewed the results of questionnaires sent to stakeholders and to staff of the Health Protection Branch;
- Met with the head of the Therapeutic Products Programme;
- Traveled to Washington to consult with representatives of the Food and Drug Administration and observe the public hearing process;
- Worked together by means of teleconferences and exchanges of electronic mail.

2.2 In addition, the Chair met with the TPP Management Advisory Committee early in May.

2.3 The report of the Committee on the Washington consultations is attached as Annex B to this Interim Report. Attached as Annex C are the summaries of questionnaire results. These were prepared by Russ Graham, and the Committee suggests strongly that all SAB members review them thoroughly. We would also like to thank Russ for his diligence in preparing them.

3. Method of Analysis

3.1 For the purposes of this Interim Report, we have identified four principles as essential to consideration of the drug review process. These are:

- Timeliness;
- Transparency;
- Efficiency;
- Effectiveness.

While these are interactive, we will review them as separate headings.

3.2 We have also identified four further considerations that in one way or another impinge on these principles. These are:

- User fees;
- Post-market surveillance;
- International harmonization;
- Orphan products.

These will be referred to in the discussions of the four principles listed above.

4. Discussion

4.1 Timeliness

4.1.1 Some of the public controversy that has beset the HPB in recent years has been rooted in questions regarding the timeliness of the drug review process. Dissatisfaction regarding the application of this principle to the scientific work essential to the process in Canada seems virtually universal, but for significantly different reasons. Broadly, drug manufacturers believe the process takes too long. Consumers and advocacy groups fear that scientific investigators are under pressure, direct or indirect, to speed up the process to a point that may endanger public safety. Some others fear that new products urgently needed for life-threatening conditions are being unduly delayed.

4.1.2 Where there is agreement, it is that the process in Canada takes significantly longer than in other jurisdictions that can be considered roughly comparable, notably the United States. The argument is made by HPB management that much of the reason for this is due to backlog, and that once an application is actually reviewed—as distinct from merely received—the Canadian process is rather more like that of our

counterparts in terms of timeliness. This backlog is usually ascribed to inadequate resources.

4.1.3 In some jurisdictions, such as the United Kingdom, the time allowed for at least some aspects of the drug review process is set by statute. In the United States, the *Prescription Drug User Fee Act* almost amounts to a treaty between the prescription drug manufacturers and the government, ensuring that the prompt payment of a substantial fee guarantees that resources will be adequate for speedy review. We consider it significant that statutory time limits and user fees raise very vexing questions, even if we set aside completely for the moment the inevitable considerations of public confidence in the process.

4.1.4 Take statutory time limits. Little if any room is allowed for the difference between an application requiring complex and extensive study, and something relatively straightforward. If fixed durations for evaluation are specified--*n*-days for a routine application; $n+x$ for something agreed to be more complex--then the special requirements of an application for a particularly complicated or potentially hazardous drug are given no weight. Quality of scientific investigation must inevitably be compromised in at least some cases. Where a complex schedule of varying statutory time limits is proposed, one must consider the considerable likelihood that the applicant will be tempted to describe the application in terms that meet the shortest time limit, however inappropriate. A first-come-first-served policy is essential if such a system is to be used and this weakens the capacity of management to assign priority to a product whose introduction may have the most important implications.

4.1.5 User fees, in Canada called *cost recovery*, present rather a different array of considerations. They have been used here for some years, but it should be noted that the Canadian system has little resemblance to its U.S. counterpart. For FDA purposes, user fees are:

- Applicable only to applications for prescription drugs by companies responsible for innovator-research (not generics);
- Go into an earmarked fund outside the jurisdiction or control of the Treasury;
- Can only be collected if allocations of public funds voted by Congress do not fall below a specific level.

This system has proved successful for FDA and manufacturers applying in the United States.

4.1.6 Further, the US user fee system has other difficulties. Among them are:

- Creation of two kinds of organizations within the administrative-regulatory agency—those dependent upon only appropriations and those with access to appropriations and to user fees;
- Creation of two categories of applicants—those who believe they have a semi-contractual relationship with the agency, (since they pay fees) and those without such an understanding (and who do not pay fees);
- Emphasis on pre-licensing research at the risk of detriment to post-market surveillance;
- Risk of skewed priorities; especially towards *orphan products.*

Regarding the first point: the FDA experience indicates that special provisions to enhance pay and benefits beyond normal government maximums risks having user-fee supported research become a sort of black hole, sucking in the best talent at the cost of other activities. Regarding the second, SAB members are referred to the report *USER FEES: Where does the buck stop?* appended to the Merck-Frosst response to our questionnaire, which makes it quite clear that industry expected certain benefits and hasn't received them. Regarding the third point: post-market surveillance has emerged in our work as a major concern, and it is difficult in a user-fee environment to judge how such fees could provide adequate resources -- as users who provide the fees understandably want their contributions to go to the approval process. Other funding approaches may be needed.

Finally, while we were impressed with the Orphan Products Program of FDA (see 3.3.1 – 3.3.3 of our Washington report), its very existence and its provisions indicate that extraordinary measures had to be implemented if the drug manufacturers were to be persuaded to address this area; and one of those provisions is exemption from user fees.

4.2 Transparency

4.2.1 A major reason for visiting Washington was to experience directly the public hearing process, so often referred to in responses to our questionnaire. Interestingly, while public hearings are most often called for by advocacy groups, concern with *transparency* is also expressed by industry. The problem, of course, is that industry at the same time seeks to protect its commercial intellectual property rights.

4.2.2 What we observed in Washington is described in paragraphs 2.1 – 2.4 of our Washington report. No observer can fail to be struck by the fact that the same companies that insist on secrecy when it comes to their applications in Canada are

perfectly prepared to send senior scientific and management representatives to public hearings in Washington, there to present details of their research and to answer detailed questions on the science supporting their applications to the FDA. No limits are put on the circulation of information presented at the FDA public hearings—the material is immediately posted on the Internet, and three video companies individually record the proceedings and sell cassettes commercially. The inconsistency between American and Canadian process in this regard cannot be overemphasized. We shall return to this in our Final Report, but for the moment we would raise with colleagues from Health Canada whether such transparency is possible under existing Canadian law, and whether the legal review process now under way contemplates any change or clarification of law that might be needed to permit or encourage such a process.

4.2.3 This area is an obvious candidate for serious effort at international harmonization. We noted that USFDA hearings are public only in a limited sense, despite the Internet postings and the other information activities. For one thing, they take place almost only in the Washington area, in locations selected more for administrative convenience than public access, and the FDA alone selects which drug approval applications are presented for public hearing. For another, the discussions at times move well beyond the grasp of lay people, and there seemed little effort during the hearings themselves to at least provide occasional summaries in plain language of the details at issue. We noted with interest, however, that very serious efforts are made to assist representatives of consumer organizations to participate.

4.2.4 Finally, we note that transparency of process is the other great source of friction and controversy surrounding the work of the HPB, and the consequent decline in public confidence. This is a constant and almost universal theme in the replies to our questionnaire. Unless the scientific work of the HPB can be seen to be comprehensive, rigorous, adequately funded, and free from external influences, the current low level of confidence might dip even lower.

4.3 Efficiency

4.3.1 We noted above, and in our Washington report, that the move to prescription drug user fees in the FDA process is described as having improved efficiency in reviewing drug applications. But we also noted that the U.S. system is probably unique to that country, and the characteristics that make it successful probably cannot be replicated in Canada. At this point, it is unclear whether user fees now imposed in Canada have improved the efficiency of the drug review process in HPB. The study being

undertaken by outside consultants on behalf of TPP will presumably cast light on this issue.

4.3.2 Other management practices may be rather more promising. We noted that the FDA simply will not accept an application that is incomplete or does not fully match its well publicized standards, and no doubt this is one of the reasons for its record of timeliness.

4.3.3 The role of post-market surveillance in improving efficiency should not be overlooked. A full, properly funded program whose results are widely known will improve both the quality of applications and the thoroughness of investigation, to the inevitable benefit of efficiency. Where applicants know that their applications will be measured against pertinent results of post-market surveillance, and that approved products will be similarly scrutinized when they come on the market, they will be motivated to prepare applications accordingly; and the inevitably improved applications will ensure that the review process is comparably more efficient: better input means better output.

4.3.4 Excellence in science is a contributor to the drug review process. The Final Report will provide some commentary on this. To date, much of the reason offered for restricting the scientific life of HPB professional staff has been rooted in the concern for commercial confidentiality. As noted in 4.2.2 above, much of this concern may be without foundation.

4.4 Effectiveness

4.4.1 At present, the drug review process seems exclusively a product-by-product, application-by-application system. A better grip on the *effectiveness* of the system might well be based in broad research programs seeking to investigate the effects over time of families of related products, or of products seeking to address identical or similar problems, or at least seeking to achieve similar effects.

4.4.2 We noted in 4.3.3 above the role of post-market surveillance in improving the efficiency of the drug review process. It also appears that post-market surveillance may be the weakest part of the current drug review process in verifying the effectiveness of specific drug products. We noted that the FDA process is impressive in getting new products to market, but the emphasis on user-fees and the dual-

category system it creates seems to overwhelm the necessary research to ascertain what happens with such new products when they become widely used by the general public.

5. Conclusions

5.1 The Committee has found its work so far to be challenging. Much of it has involved synthesis, because a great deal of information is available, although typically in fragmented form and scattered through many sources.

5.2 We plan to continue to consult with stakeholders, including the management and staff of the Health Protection Branch, and we wish to acknowledge and give thanks for the information and advice already received.

5.3 We are at this point confident of meeting our target of putting before the SAB a Final Report at the scheduled November meeting.

Drug Review Process Committee
October 29, 1999

Appendix E

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Appendix F

Notes on Canadian Law and the Drug Review Process

1 A consideration frequently cited in discussions of transparency in the drug review process is the legal restrictions. Industry, for business reasons, takes a restrictive view of what the law permits in the way of disclosure. In general, the Health Protection Branch has also taken a very cautious position on what it releases as public information.

2. Two types of laws apply in the drug review process. One is the constitutional law of Canada and the international treaties entered into by Canada; the other is the body of Canadian domestic law.

3. Increasing transparency in the drug review process would not create a constitutional problem.

4. As to treaty obligations, both the WTO and NAFTA contain provisions concerning the drug review process: Section 39(3) and 1711(5) respectively. The NAFTA provision is as follows:

> *"if a party requires, as a condition for approving the marketing of pharmaceutical or agricultural products that utilize new chemical entities, the submission of undisclosed test or other data necessary to determine whether the use of such products is safe and effective, the Party shall protect against disclosure of the data of persons making such submissions, where the origination of the data involves considerable effort, except where the disclosure is necessary to protect the public or unless steps are taken to ensure that the data is protected against unfair commercial use."*

Not all things must be kept secret by this clause. For example, there is no requirement to withhold the date of an application. *The article is clearly aimed at protecting confidential scientific data.* Even protected data may be released "to protect the public" or where measures are implemented to ensure that the data is not used for unfair advantage.

5. Measures to require transparency for the protection of the public are not a violation of this treaty obligation. Canada would not be the subject of any action under these treaties if we adopted procedures which were no more transparent than those of our largest trading partner, the United States. That country already has considerably more transparency than Canada, and we were made aware of no complaint against the United States under international trade agreements arising out of U.S. transparency in its drug review process.

"This is not a legal opinion of Health Canada, nor does it otherwise reflect Health Canada's views, but represents only the opinions of the Drug Review Process Committee of the Science Advisory Board"

6. In our view, wide latitude to improve transparency is permitted by these obligations, provided that there is a public interest in permitting the disclosure. *Only confidential scientific data is protected--not information which is not scientific; nor is scientific data protected where it is not confidential.* These provisions thus pose no impediment to the recommendations propose.

7. Canada's *Access to Information Act* applies, specifically subsections (a) through (c) of Section 20:

> *... the head of a government institution shall refuse to disclose any record requested under this* Act *that contains:*
>
> *(a) financial, commercial, scientific or technical information that is confidential information supplied to a government by a third party and is treated consistently in a confidential manner by the third party;*
>
> *(b) information the disclosure of which could reasonably be expected to result in material financial loss or gain to, or could reasonably be expected to prejudice the competitive position of, a third party; or*

Fortunately, there are Court decisions interpreting these clauses in the context of information regarding new drug submissions, and two cases in particularly are relevant here.

8. In the case of *Merck Frosst Canada Inc. v. Canada (Minister of Health and Welfare) (1988) F.C.J. no. 290,* the late Associate Chief Justice Jerome considered the applicant's request that certain information not be released pursuant to an Access to Information (ATI) request in respect of a new drug submission (Clinoril). It was asserted that the documents in question contained "negative, critical and prejudicial comments" concerning the drug, which questioned its safety and efficacy. It was also asserted that the documents "conveyed an image of a company who has tried to camouflage information from the public, whose testing is sloppy and whose drug is questionable". The Court found that the onus rested with the company to show that the information should not be disclosed. The Court's decision is at odds with the current procedures within TPP, which seem to enjoin secrecy unless there is a requirement that the information be disclosed. Chief Justice Jerome noted that most of the information was already publicly available in the product monograph. Although as such it was probably not the sort of information the *Act* was intended to protect, it was no longer "secret" and therefore the provision would not apply to prohibit release of the information.

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9. Importantly, the Court referred with approval to the case of *Piller Sausages & Delicatessen Limited v. Minister of Agriculture*, noting that information available in meat inspection reports from American authorities was not confidential, and that the dissemination of the product monograph was analogous. The Court also noted that allegations of competitive harm had been made by the company, with no supporting evidence. This section was also construed by the Federal Court of Appeal in an appeal from a decision of the late Associate Chief Justice in *Cyanamid Canada Inc. v. Canada (Minister of National Health and Welfare) (1992) F.C.J. No. 950 (F.C.A.)*. This case also stands for the proposition that the rights of secrecy and confidentiality fall away with the public release of the monograph.

10. From this brief review, we conclude:

- Data which is not scientific or technical is not protected;
- Information which has become public in other jurisdictions, such as the United States, through their regulatory processes is not a "secret" and not protected; and
- Even technical and scientific data which have enjoyed protection lose protected status if they are .... product monograph--public information is not protected information under the Access to Information Act.

Significant improvements in transparency can be achieved simply by interpreting the *Act* as it is meant to be interpreted: with a presumption of disclosure unless an exemption is clearly warranted.

11. If necessary, the Act can be amended as part of the legislative renewal initiative at present under way for Health Canada, to clarify that transparency reforms do not conflict with the Act; or regulations can be passed clarifying the limited application of the Act to the drug review process. Much should be disclosed under the Act upon request, but our objective should be a system whose transparency does not need to be triggered by Act requests.

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Report of a Meeting and Consultation with Stakeholders,
Science Advisory Board Drug Review Process Committee
3-4 November 1999, Ottawa
Château Cartier

3 November 1999 6:00 - 9:30

Supper was followed by an information session for meeting participants.

Present: Doug Elliott (SAB, Committee Chair),
Jean Jones (SAB),
Leslie Millin (SAB),
Russ Graham (SAB),
stakeholders:
Dr. Linda Strand, Canadian Public Health Association
Ms. Deanne Groetzinger, Multiple Sclerosis Society of Canada
Mr. William Leslie, Canadian Society of Hospital Pharmacists
Ms. Carole Rykczinski, Canadian Pharmacists Association
Mr. Jim Blackburn, Advisory Committee on Management, TPP
Ms. Janet Conners, Canadian Treatment Advocates Council
Mr. Jim Hems, Canadian Drug Manufacturers Association
Ms. Lori Potovsky-Beachell, Consumers Association of Canada
SAB Secretariat:
Hélène Quesnel, Mandy Lall, H.T. Murphy (Secretary)

Elliott introduced the session by setting out its purpose: to gather feedback for the Committee's report from key informants: active, interested stakeholders in the drug review process undertaken by the Committee. He explained the SAB, the Committee, and its arm's length relation to the Minister. He reviewed the Committee work to date. He underlined that the meeting was an information gathering and feedback session, not secret, and urged participants to share the meeting with colleagues. He also pointed out that the committee did not duplicate the TPP one, complementary rather, and destined for different audiences. He was confident he said that this report would have the Minister's attention and he trusted the Minister would act on it as he had on the SAB's recommendations to date.

He set out the topics for the next day: timeliness, transparency, efficiency, effectiveness; and the cross-cutting issues of user fees (cost recovery), post-market surveillance, orphan drugs, and international harmonization.

The committee was to prepare its report for the 23-24 November Board meeting, and Elliott undertook to send to participants the Committee's recommendations to the Board, and the Board's recommendations as a result, when the Board finalized them.

In the questions that followed Elliott said that: the Board Chair would meet with the Minister or speak with him about the recommendations, and members of the Board with his staff; the Minister then acts at his discretion. All recommendations will go forward as matters of principle regardless of price tag; the Minister is aware of this and the TPP initiative.

4 November 1999 8:00 - 4:00

Participants joining:
Ms. Gina Charos, Canadian Healthcare Association
Mr. Robert White, Nonprescription Drug Manufacturers Association of Canada

Elliott recapped the meeting's agenda, its purpose, transparency, objectives, proposed outcomes. Committee members then made presentations on issues identified in the survey of stakeholders: the drug review process's timeliness and transparency (Jones), and efficiency and effectiveness (Graham); user fees, post-market surveillance, orphan drugs, and international harmonization (Millin) were addressed after the lunch break; Elliott offered concluding remarks.

Transparency, timeliness

Jones led off by asking for comments, suggestions, recommendations and concerns around these issues. Lack of transparency, lack of information on timelines and dates of submissions were identified as some areas of concern.

In the discussion that followed, participants agreed that transparency in the drug review process was essential to the credibility of the system and the confidence of the consumer. "Transparency" included accessible, understandable, inclusive, consistent, timely information at all stages and at levels of content useful to all stakeholders and the general public, on reviews of both compliant and non-compliant drugs. (A transparent system would by its nature be timely.)

Issues raised: how to have accessible information and protect proprietary data; how to assure the opportunity for public input (public hearings?); how to assure timeliness and broad consultation; and the role if any of expert advisory committees.

It was agreed that a made-in-Canada system addressing these issues was possible and that other jurisdictions could offer some models to build on.

After health-break there was discussion of labelling, patient monographs, drug updates: essentially, communications with the public. It was agreed updates were essential; labelling could be improved; patient monographs were important and should be standardized and widely shared for patients' sake, perhaps through a national agency.

The discussion returned to the timeliness issue. It was agreed that the present backlog was a major obstacle to timeliness and must be cleared, using whatever resources were necessary. Milestones and accountability to meet them (and possible penalties if not met) were also essential. Applications it was

agreed must meet all completion criteria to be accepted by TPP.

There was discussion of if or when to "stop the clock" on applications if problems arose, and it was agreed that other jurisdictions and Canadian practice should be examined to create a model. Safety of the product was paramount in all drug review processes, not just timeliness or any other procedure.

The discussion then turned to efficiency and effectiveness (R. Graham presents). The discussion returned to timeliness as a manifestation of these two issues, for example, what length of time to propose for application review; when to "start" and "stop" the clock; what penalties for incomplete applications; rules for complex and simple applications. All agreed that resources were the obstacle, that is, lack of adequate resources (dollars and expert staff) to clear the backlog and assure timely processing of applications. New and sufficient resources must be given to TPP if it is to do its job. There was some discussion of how to clear the backlog.

The issue of user fees/cost recovery was discussed here; industry does not mind fees if it gets service, but fees cannot provide the resources necessary to clear the backlog and assure timelines. There was scattered discussion of parallel/sequential review (not a problem); Schedule F ("get rid of it"); priority review not an issue in a transparent, timely, adequately-resourced system, but must respond flexibly to new threats and opportunities); usefulness of other jurisdiction's models (take the best from all); contracting out (possible conflicts of interest, permanent staff are essential); special agency vs. TPP (can be flexible inside the existing government framework).

The meeting then turned to communications, that is public input to HPB/TPP/the drug review process. How to involve the consumer was seen as a vital and complex issue. The U.S. FDA model was discussed, and the absence of formal consumer representatives in the existing process in Canada. The HPB's proposed OCAPI was discussed and its potential to inform and train consumers as well as to act as a source of information. An unshakeable commitment to transparency would automatically produce proactive communications. A caution was expressed that government training of consumer representatives could be viewed as cooptation; discussion of how best to provide consumer and patient input followed but with no resolution. It was agreed that consumer groups did make themselves known to government so they were already a very aware and articulate public representative but individuals had no access. OCAPI and consumer/patient representatives could provide this access but both needed adequate resources if they were to do so successfully.

After lunch break Elliott again thanked the participants (some were leaving early) and invited them to forward concerns and remarks from the meeting.

The topics for discussion now were user fees, post-market surveillance, orphan drugs, and international harmonization (L. Millin presents). He reviewed the Canadian, U.S., U.K. and E.U. experience. It was suggested that while a huge sum in user fees is collected annually, the government doesn't deliver value for the fees, which don't go back into the DRP. ("Cost recovery" and "user fees" were the same for the purposes of this discussion.) It was agreed that there was unhappiness and confusion over user fees which do not provide value to the system and until they do there would be no acceptance of them. Further, fees are seen by consumers as a possible source of conflict between their best interests

hopefully represented by government, and industry. Confidence in this process needs to be established. Again, adequate resourcing by government of the DRP would help reestablish confidence in the process. Fees should go back into the process, which itself should be timely, transparent and accountable.

There was discussion of the appropriate ratio of fees to funding, of fees as part of an accountability régime (not resolved), and of performance measurement and rewards. It was requested that the SAB through the SAB DRP committee ask the Minister to review cost recovery with the Treasury Board, taking meeting comments into consideration.

On post-approval monitoring, participants noted that the subject had been "studied to death", the recommendations were there, it was time to implement them. Though it was acknowledged no régime does post-approval monitoring satisfactorily, Canada could take a leadership role: "Get on with it." Discussion of what an Adverse Drug Reaction (ARD) was in the real population (need for new definitions); how to assure ADRs are captured, monitored, and reported; that is, a communications and reporting process was needed; it was suggested that TPP coordinate, integrate and share information on ADRs with all partners, eg doctors, nurses, pharmacists, the drug manufacturing industry, the provinces, consumer groups, etc to assure a model post-approval monitoring process.

Again, it was noted that more and adequate resources were essential to make post-approval monitoring effective. Bill C-6 was noted here as a potential concern with regards to the free flow of such data; Elliott said the SAB had drawn this to the Minister's attention, for discussion with the Bill's sponsor Minister Manley.

The issue of orphan drugs was then discussed. Elliott reviewed various régimes' approach to orphan drugs and said if government were to get involved with such a program, it could do so by way of changes to legislation; but in such a way as to avoid conflicts of interest. Some suggested piggybacking on other régimes' expertise and developing a Canadian niche of expertise; Elliott said that perhaps it could be overseen by Health Canada but managed by say the Medical Research Council. The discussion did not recommend on whether an orphan drug program was needed in Canada.

Next discussed was international harmonization. Millin reviewed Canada's participation in efforts at IH, and the U.S. and E.U. positions. It has been suggested he said that if three or four jurisdictions similar to Canada's accept a product, Canada could and without further ado. In any case Canada as a smallish and not over-rich country could not possibly review all the thousands of products brought to market each year.

Elliott suggested that perhaps the backlog could be thinned if applications in it for drugs which had been cleared by other acceptable jurisdictions were OKed. Some participants agreed with this latter, and the meeting noted that while international harmonization should be pursued, so should internal harmonization, and it was recommended that internal harmonization (ie between and among the federal and provincial governments) to assure consumers got the approved products with the least delay. There was some discussion of drug pricing but recommendations were not made.

Elliott concluded the meeting with thanks to all and a repeated invitation to share the meeting with their colleagues; and he assured them that the committee would share its report and recommendations with them as soon as possible. He concluded by expressing his optimism that positive change would be effected in the DRP as a result of their shared work.

SUMMARY

Resources: Lack of resources adequate to do a proper job of drug evaluation in Canada was noted and deplored throughout the meeting. All the issues on the agenda in one way or another would be solved and addressed if sufficient resources – dollars and expert staff – were applied to them.

Transparency: It was agreed that lack of transparency in the process had led to a loss of confidence in it, and that all efforts must be made to establish a process transparent to all participants and stakeholders including the general public. Excellent communications was an essential tool in this transparent process.

Timeliness was seen to depend on adequate resources.

Efficiency and effectiveness were part of the timeliness issue, dependent on adequate resources.

User fees / cost recovery were not seen to be an obstacle except insofar as they had added to the erosion of confidence in the process, through the perception of collusion or conflicts of interest; fees had to be seen to be adding value to the process which they did not seem to do. They were also not to replace adequate resourcing of the process by the government.

Communications, that is assuring the involvement and the input of the public in the process and a two-way constant and consistent flow of information between and among all stakeholders and the DRP, was seen as essential to the drug review process's credibility.

Post approval monitoring has been extensively discussed and the government should act now to put the existing recommendations into effect, establishing Canada as a leader in this field. Again adequate resourcing would be essential to success here.

Orphan drugs were reviewed and while it was agreed orphan drugs were needed, there was no firm recommendation on how to go about establishing a Canadian program; perhaps Canada could piggy back on US initiatives and perhaps develop a Canadian "niche" for such products, perhaps sponsored by HC but managed by an outside agency like the MRC.

International harmonization similarly was seen to be important but no firm recommendations emerged; it should be pursued however, and equally important, it was recommended that internal harmonization be undertaken.

Appendix H

COUNCIL OF THE EUROPEAN UNION

Brussels, 27 September 1999 (OR. en)

9616/1/99 REV 1

LIMITE

ECO 241 SAN 98 CODEC 380

Interinstitutional File: 98/0240 (COD)

COMMON POSITION (EC) NO /1999

ADOPTED BY THE COUNCIL ON 27 SEPTEMBER 1999

WITH A VIEW TO THE ADOPTION

OF REGULATION (EC) NO /1999

OF THE EUROPEAN PARLIAMENT

AND OF THE COUNCIL

ON ORPHAN MEDICINAL PRODUCTS

REGULATION (EC) No /1999 OF THE EUROPEAN PARLIAMENT AND OF THE COUNCIL

of

on orphan medicinal products

THE EUROPEAN PARLIAMENT AND THE COUNCIL OF THE EUROPEAN UNION,

Having regard to the Treaty establishing the European Community, and in particular Article 95 thereof,

Having regard to the proposal from the Commission [1],

Having regard to the Opinion of the Economic and Social Committee [2],

Acting in accordance with the procedure laid down in Article 251 of thTreaty [3],

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1 OJ C 276, 4.9.1998, p. 7 and OJ C .

2 OJ C 101, 12.4.1999, p. 37.

3 Opinion of the European Parliament of 9 March 1999 (OJ C 175, 21.6.1999, p. 61), Council Common Position (not yet published in the Official Journal) and Decision of the European Parliament (not yet published in the Official Journal).

Whereas:

(1) Some conditions occur so infrequently that the cost of developing and bringing to the market a medicinal product to diagnose, prevent or treat the condition would not be recovered by the expected sales of the medicinal product; the pharmaceutical industry would be unwilling to develop the medicinal product under normal market conditions; these medicinal products are called "orphan";

(2) Patients suffering from rare conditions should be entitled to the same quality of treatment as other patients; it is therefore necessary to stimulate the research, development and bringing to the market of appropriate medications by the pharmaceutical industry; incentives for the development of orphan medicinal products have been available in the United States since 1983 and in Japan since 1993;

(3) In the European Union, only limited action has been taken so far, whether at national or at Community level, to stimulate the development of orphan medicinal products; such action is best taken at Community level in order to take advantage of the widest possible market and to avoid the dispersion of limited resources; action at Community level is preferable to uncoordinated measures by the Member States which may result in distortions of competition and barriers to intra-Community trade;

(4) Orphan medicinal products eligible for incentives should be easily and unequivocally identified; it seems most appropriate to achieve this result through the establishment of an open and transparent Community procedure for the designation of potential medicinal products as orphan medicinal products;

(5) Objective criteria for designation should be established; those criteria should be based on the prevalence of the condition for which diagnosis, prevention or treatment is sought; a prevalence of not more than five affected persons per ten thousand is generally regarded as the appropriate threshold; medicinal products intended for a life-threatening, seriously debilitating or serious and chronic condition should be eligible even when the prevalence is higher than five per ten thousand;

(6) A Committee composed of experts appointed by the Member States should be established to examine applications for designation; this Committee should also include three representatives of patients' associations, designated by the Commission, and three other persons, also designated by the Commission, on a recommendation from the European Agency for the Evaluation of Medicinal Products; the Agency should be responsible for the adequate coordination between the Committee on orphan medicinal products and the Committee on proprietary medicinal products;

(7) Patients with such conditions deserve the same quality, safety and efficacy in medicinal products as other patients; orphan medicinal products should therefore be submitted to the normal evaluation process; sponsors of orphan medicinal products should have the possibility of obtaining a Community authorisation; in order to facilitate the granting or the maintenance of a Community authorisation, fees to be paid to the Agency should be waived at least in part; the Community budget should compensate the Agency for the loss in revenue thus occasioned;

(8) Experience in the United States and Japan shows that the strongest incentive for industry to invest in the development and marketing of orphan medicinal products is where there is a prospect of obtaining market exclusivity for a certain number of years during which part of the investment might be recovered; data protection under Article 4(8)(a)(iii) of Council Directive 65/65/EEC of 26 January 1965 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal

products [1] is not a sufficient incentive for that purpose; Member States acting independently cannot introduce such a measure without a Community dimension as such a provision would be contradictory to Directive 65/65/EEC; if such measures were adopted in an uncoordinated manner by the Member States, this would create obstacles to intra-Community trade, leading to distortions of competition and running counter to the single market; market exclusivity should however be limited to the therapeutic indication for which orphan medicinal product designation has been obtained, without prejudice to existing intellectual property rights; in the interest of patients, the market exclusivity granted to an orphan medicinal product should not prevent the marketing of a similar medicinal product which could be of significant benefit to those affected by the condition;

(9) Sponsors of orphan medicinal products designated under this Regulation should be entitled to the full benefit of any incentives granted by the Community or by the Member States to support the research and development of medicinal products for the diagnosis, prevention or treatment of such conditions, including rare diseases;

(10) The specific programme Biomed 2, of the fourth Framework Programme for research and technological development (1994-1998), supported research on the treatment of rare diseases, including methodologies for rapid schemes for the development of orphan medicinal products and inventories of available orphan medicinal products in Europe; those grants were intended to promote the establishment of cross national co-operation in order to implement basic and clinical research on rare diseases; research on rare diseases continues to be a priority for the Community, as it has been included in the fifth Framework Programme for research and technological development (1998-2002); this Regulation establishes a legal framework which will allow the swift and effective implementation of the outcome of this research;

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[1] OJ L 22, 9.2.1965, p. 369. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).

(11) Rare diseases have been identified as a priority area for Community action within the Framework for Action in the field of public health; the Commission, in its communication concerning a programme of Community action on rare diseases within the Framework for Action in the field of public health has decided to give rare diseases priority within the public health framework; the European Parliament and the Council have adopted Decision No 1295/1999/EC of 29 April 1999 adopting a programme of Community action on rare diseases within the framework for action in the field of public health (1999-2003) [1], including actions to provide information, to deal with clusters of rare diseases in a population and to support relevant patient organisations; this Regulation implements one of the priorities laid down in this programme of action,

HAVE ADOPTED THIS REGULATION:

Article 1

Purpose

The purpose of this Regulation is to lay down a Community procedure for the designation of medicinal products as orphan medicinal products and to provide incentives for the research, development and placing on the market of designated orphan medicinal products.

[1] OJ L 155, 22.6.1999, p. 1.

Article 2

Definitions

For the purposes of this Regulation:

(a) "medicinal product" means a medicinal product for human use, as defined in Article 2 of Directive 65/65/EEC;

(b) "orphan medicinal product" means a medicinal product designated as such under the terms and conditions of this Regulation;

(c) "sponsor" means any legal or natural person, established in the Community, seeking to obtain or having obtained the designation of a medicinal product as an orphan medicinal product;

(d) "Agency" means the European Agency for the Evaluation of Medicinal Products.

Article 3

Criteria for designation

1. A medicinal product shall be designated as an orphan medicinal product if its sponsor can establish:

(a) that it is intended for the diagnosis, prevention or treatment of a life-threatening or chronically debilitating condition affecting not more than five in ten thousand persons in the Community when the application is made, or

(b) that it is intended for the diagnosis, prevention or treatment of a life-threatening, seriously debilitating or serious and chronic condition in the Community and that without incentives it is unlikely that the marketing of the medicinal product in the Community would generate sufficient return to justify the necessary investment;

(c) and that there exists no satisfactory method of diagnosis, prevention or treatment of the condition in question that has been authorised in the Community or, if such method exists, that the medicinal product will be of significant benefit to those affected by that condition.

2. The Commission shall adopt the necessary provisions for implementing this Article in the form of an implementing Regulation in accordance with the procedure laid down in Article 72 of Council Regulation (EEC) No 2309/93 [1].

Article 4

Committee for Orphan Medicinal Products

1. A Committee for Orphan Medicinal Products, hereinafter referred to as "the Committee", is hereby set up within the Agency.

2. The task of the Committee shall be:

(a) to examine any application for the designation of a medicinal product as an orphan medicinal

[1] OJ L 214, 24.8.1993, p. 1. Regulation as amended by Commission Regulation (EC) No 649/98 (OJ L 88, 24.3.1998, p. 7).

product which is submitted to it in accordance with this Regulation,

(b) to advise the Commission on the establishment and development of a policy on orphan medicinal products for the European Union,

(c) to assist the Commission in liaising internationally on matters relating to orphan medicinal products, and in liaising with patient support groups;

(d) to assist the Commission in drawing up detailed guidelines.

3. The Committee shall consist of one member nominated by each Member State, three members nominated by the Commission to represent patients' organisations and three members nominated by the Commission on the basis of a recommendation from the Agency. The members of the Committee shall be appointed for a term of three years, which shall be renewable. They may be accompanied by experts.

4. The Committee shall elect its Chairman for a term of three years, renewable once.

5. The representatives of the Commission and the Executive Director of the Agency or his representative may attend all meetings of the Committee.

6. The Agency shall provide the Secretariat of the Committee.

7. Members of the Committee shall be required, even after their duties have ceased, not to disclose any information of the kind covered by the obligation of professional secrecy.

Article 5

Procedure for designation and removal from the register

1. In order to obtain the designation of a medicinal product as an orphan medicinal product, the sponsor shall submit an application to the Agency at any stage of the development of the medicinal product before the application for marketing authorisation is made.

2. The application shall be accompanied by the following particulars and documents:

   (a) name or corporate name and permanent address of the sponsor,

   (b) active ingredients of the medicinal product,

   (c) proposed therapeutic indication,

   (d) justification that the criteria laid down in Article 3(1) are met and a description of the stage of development, including the indications expected.

3. The Commission shall, in consultation with the Member States, the Agency and interested parties, draw up detailed guidelines on the required format and content of applications for designation.

4. The Agency shall verify the validity of the application and prepare a summary report to the Committee. Where appropriate, it may request the sponsor to supplement the particulars and documents accompanying the application.

5. The Agency shall ensure that an opinion is given by the Committee within ninety days of the receipt of a valid application.

6. When preparing its opinion, the Committee shall use its best endeavours to reach a consensus. If such a consensus cannot be reached, the opinion shall be adopted by a majority of two-thirds of the members of the Committee. The opinion may be obtained by written procedure.

7. Where the opinion of the Committee is that the application does not satisfy the criteria set out in Article 3(1), the Agency shall forthwith inform the sponsor. Within ninety days of receipt of the opinion, the sponsor may submit detailed grounds for appeal, which the Agency shall refer to the Committee. The Committee shall consider whether its opinion should be revised at the following meeting.

8. The Agency shall forthwith forward the final opinion of the Committee to the Commission, which shall adopt a decision within thirty days of receipt of the opinion. Where, in exceptional circumstances, the draft decision is not in accordance with the opinion of the Committee, the decision shall be adopted in accordance with the procedure laid down in Article 73 of Council Regulation (EEC) No 2309/93. The decision shall be notified to the sponsor and communicated to the Agency and to the competent authorities of the Member States.

9. The designated medicinal product shall be entered in the Community Register of Orphan Medicinal Products.

10. Each year the sponsor shall submit to the Agency a report on the state of development of the designated medicinal product.

11. To have the designation of an orphan medicinal product transferred to another sponsor, the holder of the designation shall make specific application to the Agency. In consultation with the Member States, the Agency and interested parties, the Commission shall draw up detailed guidelines on the form in which applications for transfer shall be made and the content of such applications and all the particulars of the new sponsor.

12. A designated orphan medicinal product shall be removed from the Community Register of Orphan Medicinal Products:

(a) at the request of the sponsor;

(b) if it is established before the market authorisation is granted that the criteria laid down in Article 3 are no longer met in respect of the medicinal product concerned;

(c) at the end of the period of market exclusivity as laid down in Article 8.

Article 6

Protocol assistance

1. The sponsor of an orphan medicinal product may, prior to the submission of an application for marketing authorisation, request advice from the Agency on the conduct of the various tests and trials necessary to demonstrate the quality, safety and efficacy of the medicinal product, in accordance with Article 51(j) of Council Regulation (EEC) No 2309/93.

2. The Agency shall draw up a procedure on the development of orphan medicinal products, covering regulatory assistance for the definition of the content of the application for authorisation within the meaning of Article 6 of Council Regulation (EEC) No 2309/93.

Article 7

Community marketing authorisation

1. The person responsible for placing on the market an orphan medicinal product may request that authorisation to place the medicinal product on the market be granted by the Community in accordance with the provisions of Regulation (EEC) No 2309/93 without having to justify that the medicinal product qualifies under Part B of the Annex to that Regulation.

2. A special contribution from the Community, distinct from that provided for in Article 57 of Regulation (EEC) No 2309/93, shall be allocated every year to the Agency. The contribution shall be used exclusively by the Agency to waive, in part or in total, all the fees payable under Community rules adopted pursuant to Regulation (EEC) No 2309/93. A detailed report of the use made of this special contribution shall be presented by the Executive Director of the Agency at the end of each year. Any surplus occurring in a given year shall be carried forward and deducted from the special contribution for the following year.

3. The marketing authorisation granted for an orphan medicinal product shall cover only those therapeutic indications which fulfil the criteria set out in Article 3. This is without prejudice to the possibility of applying for a separate marketing authorisation for other indications outside the scope of this Regulation.

Article 8

Market exclusivity

1. Where a marketing authorisation in respect of an orphan medicinal product is granted pursuant to Regulation (EEC) No 2309/93 or where all the Member States have granted marketing authorisations in accordance with the procedures for mutual recognition laid down in Articles 7 and 7a of Directive 65/65/EEC or Article 9(4) of Council Directive 75/319/EEC of 20 May 1975 on the approximation of provisions laid down by law, regulation or administrative action relating to medicinal products [1], and without prejudice to intellectual property law or any other provision of Community law, the Community and the Member States shall not, for a period of ten years, accept another application for a marketing authorisation, or grant a marketing authorisation or accept an application to extend an existing marketing authorisation, for the same therapeutic indication, in respect of a similar medicinal product.

2. This period may however be reduced to six years if, at the end of the fifth year, it is established, in respect of the medicinal product concerned, that the criteria laid down in Article 3 are no longer met, inter alia where it is shown on the basis of available evidence that the product is sufficiently profitable not to justify maintenance of market exclusivity. To that end, a Member State shall inform the Agency that the criterion on the basis of which market exclusivity was granted may not be met and the Agency shall then initiate the procedure laid down in Article 5. The sponsor shall provide the Agency with the information necessary for that purpose.

3. By way of derogation from paragraph 1, and without prejudice to intellectual property law or any other provision of Community law, a marketing authorisation may be granted, for the same therapeutic indication, to a similar medicinal product if:

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[1] OJ L 147, 9.6.1975, p. 13. Directive as last amended by Council Directive 93/39/EEC (OJ L 214, 24.8.1993, p. 22).

(a) the holder of the marketing authorisation for the original orphan medicinal product has given his consent to the second applicant, or

(b) the holder of the marketing authorisation for the original orphan medicinal product is unable to supply sufficient quantities of the medicinal product, or

(c) the second applicant can establish in the application that the second medicinal product, although similar to the orphan medicinal product already authorised, is safer, more effective or otherwise clinically superior.

4. The Commission shall adopt definitions of "similar medicinal product" and "clinical superiority" in the form of an implementing Regulation in accordance with the procedure laid down in Article 72 of Regulation (EEC) No 2309/93.

5. The Commission shall draw up detailed guidelines for the application of this Article in consultation with the Member States, the Agency and interested parties.

Article 9

Other incentives

1. Medicinal products designated as orphan medicinal products under the provisions of this Regulation shall be eligible for incentives made available by the Community and by the Member States to support research into, and the development and availability of, orphan medicinal products and in particular aid for research for small and medium-sized undertakings provided for in framework programmes for

research and technological development.

2. Before .....* the Member States shall communicate to the Commission detailed information concerning any measure they have enacted to support research into, and the development and availability of, orphan medicinal products or medicinal products that may be designated as such. That information shall be updated regularly.

3. Before ..... ** the Commission shall publish a detailed inventory of all incentives made available by the Community and the Member States to support research into, and the development and availability of, orphan medicinal products. That inventory shall be updated regularly.

Article 10

General report

Before ..... *** the Commission shall publish a general report on the experience acquired as a result of the application of this Regulation, together with an account of the public health benefits which have been obtained.

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* Six months from the date of the entry into force of this Regulation.
** Twelve months from the date of the entry into force of this Regulation.
*** Six years after the date of the entry into force of this Regulation.

Article 11

Entry into force

This Regulation shall enter into force on the day of its publication in the Official Journal of the European Communities.

It shall apply as from the date of adoption of the implementing Regulations provided for in Article 3(2) and Article 8(4).

This Regulation shall be binding in its entirety and directly applicable in all Member States.

Done at

For the European Parliament
The President

For the Council
The President

Appendix I

Recommendations of the Consultative Workshop on the Therapeutic Products Programme Drug Review Process
September 30 - October 1, 1999

Purpose:

To provide stakeholders with observations and recommendations on Canada's drug review process.

Background:

Over time various patient and consumer advocacy groups in HIV/AIDS community, have raised concerns about Canada's drug review process; specifically with regard to timeliness, transparency and a functional post-market surveillance system.

A Consultative Workshop meeting was held by Health Canada on August 12, 1998 where HIV/AIDS stakeholder groups met with representatives of the TPP to discuss the drug review process. From this meeting a Working Group was established to analyze concerns and to develop recommendations. The Working Group met on September 30, 1998. At this meeting the Working Group requested detailed information on both pre-market review and post-approval monitoring. A sub-working group was appointed from within the larger group to deal with post-market surveillance.

PricewaterhouseCoopers was commissioned by the TPP to undertake a detailed review of the pre-market process which included an assessment of 14 drug reviews, a questionnaire to the companies associated with these drugs, and staff interviews. Xerox Canada was contracted to facilitate a process to detail the steps involved in the pre-market review process. These maps are now available electronically on the Therapeutic Products Programme website (www.hc-sc.gc.ca/hpb-dgps/therapeut/quality). HDP Group Inc. had been contracted earlier by the TPP to undertake a functional review of post-approval monitoring and its report was also provided to the Working Group.

The Working Group subsequently met on January 21, May 19-20, and July 12, 1999 to review the results of these variuous studiess. During the May and July meetings, the Working Group prepared a series of recommendations which were then reviewed and ratified during a Consultative Workshop on Drug Review in Canada, August 12, 1999 with the original invitees from the August 1998. Subsequently, the recommendations from this meeting were brought forward by members of the Working Group on HIV/AIDS to a Consultative Workshop held

September 30 - October 1, 1999 with a broader spectrum of stakeholder groups. In both Consultative Workshops, the underlying message from attendees was the urgency of the situation and that Canadians are the beneficiaries of the drug review process; a process that must be accountable to the public.

The recommendations from this meeting were categorized into five areas: over-arching, timeline, transparency, best practice and post-approval monitoring. The major, over-arching recommendations are based on the conclusions of the PricewaterhouseCoopers report that the Therapeutic Products Programme had made all of the improvements in efficiency possible with the resources allocated to it. Significant improvement in submission review times or post-approval monitoring could only be made with a significant increased investment in resources.

The recommendations are as follows:

Over-Arching Recommendations

1. The Government of Canada should immediately allocate sufficient resources to enable the implementation and maintenance of the recommendations of the Working Group on HIV/AIDS.

2. Establish a Working Group, including representatives from the Working Group on HIV/AIDS to act as the oversight group in the implementation of the recommendations.

3. Change Treasury Board guidelines and Health Canada practices to ensure carryover of fees across a fiscal boundary.

4. Establish mechanisms to ensure drug submission fees are allocated for activities related to review purposes.

Timelines Recommendations

5. Refine the Therapeutic Products Programme's criteria for designating priority reviews to ensure that priority review is granted for drugs which are intended for the treatment of a life-threatening condition, or for drugs which demonstrate the potential to address serious unmet medical needs. Under these criteria the Therapeutic Products Programme should also approve applications for a fast track review if the product has an effect on a clinical or a surrogate endpoint that is reasonably likely to predict clinical benefit.

6. Ensure adequate resourcing of review divisions with individuals having the necessary qualifications and expertise.

7. Ensure resources from one division are not depleted to augment resources in other review divisions.

8. Establish and implement mandatory time frames for review performance for a quality review with appropriate mechanisms for ensuring accountability. In recognition of the variation in the complexity of drug submissions, there is a need for different time frames depending upon the drug class. Time frames should be reduced over time as long as the quality of review is not compromised.

9. Change Therapeutic Products Programme policies and structures to allow for rolling submissions and reviews.

10. Pursue joint reviews with other jurisdictions.

Transparency Recommendations

11. Increase transparency of the review process to include access to non-proprietary information about the status of the review and the rationale for any final decision made by Therapeutic Products Programme including Notice of Non-compliance (NON), Notice of Compliance (NOC), Notice of Compliance with Conditions (NOCC), and Notice of Deficiency (NOD). Develop a meaningful system of external communication to increase the transparency of the review process with all stakeholders.

12. Consider and explore of the advisability and feasibility of including other external stakeholder input on the merits of the submission should be undertaken.

13. Re-examine all aspects of the Terms of Reference of all Expert Advisory Committees and amend as necessary to ensure effectiveness, efficiency, transparency and accountability.

Best Practices Recommendations

14. Identify best practices in use and adopt them broadly across the organization. Illustrative examples of best practices include setting clear deadlines for the completion of reviews, ensuring the timely availability of managers or panels to assess reviews, the consistent use of clarifaxes, teams, and the timely resolution of product monograph issues.

15. Ensure procedures are in place within Therapeutic Products Programme to facilitate access for sponsors throughout the review process.

16. Encourage and enhance where appropriate the application of Therapeutic Products Programme's contracting out policy in the context of the Government of Canada conflict of interest guidelines.

17. Implement current guidelines to ensure that Chemistry and Manufacturing reviews are carried out concurrently with Safety and Efficacy reviews to improve the overall review times.

Post-Approval Monitoring

18. Develop a Post-Approval Monitoring System (PAMS) which is consumer-centered and includes effective reporting mechanisms from consumers and health care professionals.

19. Ensure as a critical first step in the implementation of a Post-Approval Monitoring System (PAMS) that the data management system adapted is robust and will accommodate the increased numbers and timeliness needs of the reports.

20. Develop a PAMS which meets Canadian needs (e.g. Canadian database, develop Canadian strategies for data collection).

21. Adopt and implement the Therapeutic Products Programme's Post-Approval Assessment Strategy by 2003.

22. Ensure the Federal/Provincial/Territorial Pharmaceutical Issues Committee is made aware of the PAMS activities and encourage joint activities, where appropriate.

23. Develop a system which is open and transparent and includes an advisory body that consists of a broad spectrum of stakeholders including consumer representation. The advisory body will provide advice on the activities of the Therapeutic Products Programme's PAMS. The PAMS process itself will respect individual confidentiality.

24. Provide accounting for yearly Drug Information Number (DIN) renewal fees and ensure that an appropriate percentage of these fees is allocated to the PAMS according to original and ongoing agreements.

25. Enhance and track the Therapeutic Products Programme's PAMS activity in the curriculum of medical and other health care professional schools, and continuing education of health care practitioners.

26. Develop and implement a variety of effective strategies for soliciting adverse and other drug reaction information from consumers (local/regional/national).

27. Develop and implement a variety of effective strategies for soliciting adverse and other drug reaction information from health care professionals (local/regional/national).

28. Ensure an effective mechanism to broadly disseminate adverse drug reaction (ADR) information to all stakeholders.

29. Encourage international liaison on drug safety issues.

October 26, 1999.

GLOSSARY

Cost recovery - a policy of the Treasury Board of Canada through which departments or agencies seek to recover some of their costs where their activities are deemed to have created some measure of "private good", as compared with a "public good".

"Down time" - the term used by TPP to describe the time interval between receipt of a new drug application and the moment that the application begins the review process.

DRP - Drug Review Process

EMEA - standard acronym for the European Agency for the Evaluation of Medicinal Products, of the European Union

FDA - Food and Drug Administration of the United States of America

HPB - Health Protection Branch of Health Canada

Harmonization - the process of seeking and applying common measures or standards across jurisdictional boundaries.

HIV - Human Immunodeficiency Virus, generally believed to be the principal cause of the Auto Immunodeficiency Syndrome, commonly called AIDS.

ICH - International Committee on Harmonization, a multi-lateral body working to establish common measures or standards.

MCA - Medicines Control Agency of the United Kingdom

NDA - New drug application.

NoC - Notice of Compliance--effectively, a document certifying approval of an NDA.

OCAPI - the proposed Office of Consumer Affairs and Public Involvement for Health Canada.

Orphan Products - a generic term for therapeutic products that are unlikely to be brought to market by ordinary commercial means, either because the potential sales are deemed too small or because the costs involved in development are unusually high. FDA's *Orphan Products Program* uses a figure of <200,000 patients within the United States as the criterion, although it will cover if necessary *any* product deemed valuable but that no

manufacturer is willing to sponsor in the ordinary way. Draft legislation for the EU uses a definition of "not more than 5 in 10,000 [patients] within the Community", but it, too, is intended to cover any useful product that will not become available in the ordinary way.

OPP - FDA's *Orphan Products Program,* providing a blend of incentives to develop and bring to market orphan products. It has been the prototype for a similar program in Japan, and for the EU's intended program.

Post-market (post-approval) surveillance - the process by which therapeutic products, once approved for use, are monitored for safety and effectiveness.

SAB - Science Advisory Board of Health Canada.

TPP - Therapeutic Products Programme, the administrative unit of HPB that oversees the DRP.

Transparency - attributes of an administrative process that allow the interested observer to determine how, why, when and on what evidence decisions are made within the process.